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Special Article

ABRAMEDE clinical practice guidelines for the management of dengue in adult emergency department patients

Diretrizes clínicas da ABRAMEDE para o manejo de dengue em pacientes adultos na emergência

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ABSTRACT

In Brazil, dengue is the most significant arbovirus disease and one of the main reasons for visits in Emergency Departments. In 2024, the country has been facing a record number of cases, exacerbating the Emergency Departments overcrowding. Given the severe epidemic, it is crucial to improve clinical management to prevent the progression to severe forms of the disease and reduce mortality. This clinical guideline is dedicated to the management of adult patients with suspected or confirmed dengue in the emergency setting, whether in hospital Emergency Departments or urgent care units. The preparation of this guideline took place between February, March, and April 2024, by a panel of 17 experts. The GRADE methodology was adopted, which involves a process including: the development of systematic reviews for prioritized questions; the assessment of the certainty of evidence; and the formulation of recommendations using the GRADE evidence-to-decision framework. The GRADE-ADOLOPMENT methodology was also used to adopt and/or adapt systematic reviews and recommendations from other applicable guidelines. Ten clinical questions were prioritized and answered, generating recommendations with varying strength and levels of evidence. This is the first guideline from *Associação Brazileira de Medicina de Emergência* that employs the GRADE methodology to provide clear and evidence-based answers to the questions considered most critical by emergency physicians in the management of adult patients with dengue in emergency settings.

Keywords: Dengue; Epidemics; Guidelines as topic; Emergencies; Emergency medical services

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RESUMO

No Brasil, a dengue é a arbovirose mais significativa e um dos principais motivos de consultas em Departamentos de Emergência. Em 2024, o país vem enfrentando um número recorde de casos, exacerbando a superlotação das emergências. Diante da grave epidemia, é crucial aprimorar o manejo clínico, para evitar a evolução para formas graves da doença e reduzir a mortalidade. Esta diretriz clínica é dedicada ao manejo de pacientes adultos com suspeita ou quadro confirmado de dengue na emergência, seja em Departamentos de Emergência hospitalares ou unidades de pronto atendimento. A elaboração desta diretriz ocorreu entre fevereiro, março e abril de 2024, por um painel de 17 especialistas. Adotou-se a metodologia GRADE, que segue um processo envolvendo: o desenvolvimento de revisões sistemáticas para as questões priorizadas; a avaliação da certeza das evidências; a formulação de recomendações utilizando o *framework* GRADE *evidence-to-decision*. A metodologia GRADE-ADOLOPMENT também foi utilizada para adotar e/ou adaptar revisões sistemáticas e recomendações de outras diretrizes aplicáveis. Dez perguntas clínicas foram priorizadas e respondidas, sendo geradas recomendações com força e nível de evidência variados. Esta é a primeira diretriz da Associação Brasileira de Medicina de Emergência que emprega a metodologia GRADE para fornecer respostas claras e baseadas em evidências às perguntas consideradas mais críticas por especialistas no manejo de pacientes adultos com dengue nas emergências.

Descritores: Dengue; Epidemias; Guias como assunto; Emergências; Serviços médicos de emergência

INTRODUCTION

Dengue is an acute febrile, systemic, and dynamic disease, endemic in various parts of the world, including Brazil, where cases are recorded throughout the year, with seasonal peaks in the hottest and rainiest periods. Caused by one of the four serotypes of the dengue virus (DENV-1, DENV-2, DENV-3, and DENV-4), belonging to the Flavivirus genus, the disease is transmitted mainly by female mosquitoes of the *Aedes aegypti* species. This vector is also responsible for the transmission of other arboviruses, such as Zika, Chikungunya, and Yellow Fever.[1-3]

Dengue virus infection can manifest clinically in various ways, ranging from oligosymptomatic forms to severe conditions in the form of shock syndrome, a potentially fatal condition.[4] Viral diversity, together with host and vector factors, influences the risk of infection, the development of the disease, and its severity. The existence of temporary cross-protection between the four DENV serotypes diminishes and disappears in the months following infection, exposing individuals in endemic areas to the risk of reinfection by any of the serotypes.[1-3]

In Brazil, dengue is of significant epidemiological importance, as evidenced by the Ministry of Health's arbovirus monitoring data. In 2023, 1,658,814 probable dengue cases were recorded, which increased dramatically in 2024, reaching 2,321,050 cases by the 12th epidemiological week.[5] The country saw a record peak in mortality due to dengue in 2023, with 1,094 deaths, a figure that continues to be alarming in 2024, with 831 deaths recorded by the end of March alone. This trend of cyclical outbreaks, with occurrences every 3 to 5 years, and the recent increase in death records highlight the seriousness of the epidemiological situation.

The leading causes of death from dengue, according to the Centers for Disease Control and Prevention (CDC), include non-recognition of the disease, prolonged unidentified shock, occult hemorrhage, volume overload, liver failure, and nosocomial infections.[6] In addition, analyzing comorbidities in critically ill patients who die reveals the presence of conditions such as cardiovascular disease, diabetes, hypertension, use of antiplatelet drugs, and pregnancy-related complications, as well as coexisting bacterial infections and other diseases, indicating the complexity of managing these patients.

Among the causes of death, failure to recognise the disease and prolonged unrecognized shock emerge as one of the most critical factors, underlining the importance of early diagnosis and appropriate management, primarily through volume replacement, a fundamental pillar in dengue treatment. This reality emphasizes the crucial need for emergency physicians to identify and intervene

immediately, establishing the importance of this guideline elaborated by the Brazilian Association of Emergency Medicine (ABRAMEDE) for managing adult dengue patients in emergency settings.

SCOPE AND PURPOSE OF THE GUIDELINE

The target audience for this guideline includes health professionals responsible for the assessment and management of adult patients (aged ≥ 18 years) treated in emergency care units (UPAs, Portuguese acronym from *Unidades de Pronto Atendimento*) or hospital Emergency Departments (EDs) who present with suspected or confirmed acute dengue virus infection. Although there are recommendations from the Ministry of Health,[4] ABRAMEDE believes there is a need to generate more specific, evidence-based recommendations focused on filling the gaps in the care of these patients in the ED. With this in mind, ABRAMEDE's Clinical Practice Guidelines Committee put together a working group to collect and analyze existing evidence on the management of adult dengue patients in the ED, following GRADE (Grading of Recommendations Assessment, Development and Evaluation),[7] a methodology recommended by the World Health Organisation (WHO) for creating clinical practice guidelines.

METHODOLOGY

Group composition

The team responsible for the guideline was made up of 16 clinicians (3 women [18.8% of total], 14 board-certified in Emergency Medicine [87.5% of total]) from different regions of Brazil (South, Southeast, North, and Northeast). Four members had experience in systematic reviews; one was a methodologist trained in the GRADE method. All group members received specific guidance on the guideline development process and participated in at least one of the panel meetings or contributed to the document drafting process.

INTERACTIONS AND PROCESSES

This guideline was developed between February, March, and April 2024 in response to the urgency of an epidemic and the need to develop an applicable guideline quickly. To create the recommendations, the GRADE methodology was adopted, which follows a step-by-step process involving (1) developing or identifying recent systematic reviews for the prioritized questions, (2) assessing the certainty of the evidence, (3) formulating recommendations using the GRADE evidence-to-decision (EtD) framework, which considers ten main domains: importance of the problem, beneficial and harmful effects, quality of the evidence, stakeholder values, balance between beneficial and harmful effects, resources, equity, acceptability and feasibility. Given this context, the methodologists organized two main meetings, focusing on discussing the crucial aspects of the GRADE EtD framework.[8]

Declaration and handling of conflicts of interest

All panel participants declared their conflicts of interest using a form standardized by ABRAMEDE's Clinical Practice Guidelines Committee. Details of this form are available in Appendix 1.

DEFINITIONS OF THE POPULATION OF INTEREST

The population of interest includes patients seen in emergency settings, whether UPAs or hospital EDs, who present with suspected or confirmed dengue. The terminology adopted is based on the 2009 WHO classification, distinguishing dengue into 'without warning signs,' 'with warning signs,' and 'severe dengue'.[9] In addition, as the population of interest in the questions mentions 'suspected or confirmed cases of dengue,' these definitions were used according to the 2024 document published by the Brazilian Ministry of Health.[4]

- **Suspected dengue case:** An individual living in or who has traveled to endemic areas, presenting with fever for 2 to 7 days and two or more of the following manifestations: nausea, vomiting, rash, myalgias, arthralgias,

headache, retro-orbital pain, petechiae, positive tourniquet test and/or leucopenia.

- **Suspected dengue case with warning signs:** Dengue case in the defervescence phase of the fever that exhibits one or more of the following signs: severe abdominal pain, persistent vomiting, fluid accumulation (ascites, pleural effusion, pericardial effusion), postural hypotension/lipothymia, significant hepatomegaly, mucosal bleeding, lethargy/irritability and/or progressive increase in haematocrit.
- **Suspected severe dengue case:** Dengue presenting with shock or respiratory distress due to severe plasma leakage, severe bleeding according to medical assessment, or severe organ impairment.
- **Confirmed dengue case:** Suspected cases can be confirmed by laboratory criteria (detection of NS1 protein, viral isolation, RT-PCR, detection of IgM ELISA, or increased antibody titers in PRNT/IH) or by clinical-epidemiological criteria, especially in scenarios of inconclusive laboratory results or impossibility of specific confirmation.

Given the similarity between dengue (DENV) and Zika (ZIKV) viruses, the possibility of cross-reaction in serological tests should be considered, which may result in an inconclusive laboratory diagnosis. In cases where specific laboratory confirmation is not possible, confirmation can be made by epidemiological link with a laboratory-confirmed case after assessing the spatial distribution of cases.

SELECTION OF PRIORITIZED QUESTIONS

During the initial phase of the guideline, all the panel members and other members of the ABRAMEDE board had the opportunity to suggest questions to be addressed according to the PICO format (population, intervention, comparison, outcomes). The focus was on addressing questions pertinent to clinicians who treat patients with suspected or confirmed dengue in emergency settings, whether in UPAs or hospital EDs.

An important consideration for the panel was the feasibility of the guidelines for emergency physicians and patients in different practice settings. The group chose to limit the number of questions to 10 (ten), taking into account the time and resources available to create a guideline following the GRADE methodology. The existence of a recent guideline from the Pan American Health Organisation (PAHO) and the WHO,[10], which allowed the GRADE ADOLOPMENT process to be applied, also facilitated the inclusion of 10 questions since 7 of them already had systematic reviews available for use in this guideline.

SELECTION OF OUTCOMES OF INTEREST

For the questions related to risk stratification and prognosis, the main outcome selected was the incidence of severe dengue. Concerning questions about therapies, the main outcome of interest was mortality. Still, other outcomes were also considered, such as the incidence of shock, volume overload, bleeding, and adverse events, varying according to the specificity of each question addressed.

EVIDENCE SYNTHESIS, QUALITY ASSESSMENT, AND DEVELOPMENT OF RECOMMENDATIONS

Of the ten questions prioritized by the panel, seven already had associated systematic reviews published alongside the 2022 WHO/PAHO guideline.[10] The synthesis of evidence from these reviews was adopted to inform the panel on these specific questions.

For the remaining three questions, which addressed the use of bedside ultrasound, vasoactive drugs, and reversal agents in managing dengue haemorrhagic shock, a detailed literature search was conducted with the help of a Mayo Clinic medical librarian with expertise in systematic reviews. The searches were conducted in February 2024 on ClinicalTrials.gov (since 2000), Ovid Cochrane Central Register of Controlled Trials (since 1991), Ovid Embase (since 1974), Ovid

Medline (since 1946, including preprints, in-process and other non-indexed citations), SciELO Citation Index (since 2002), Scopus (since 1788), Web of Science Core Collection (since 1975 for Science Citation Index Expanded and since 2015 for Emerging Sources Citation Index) and the World Health Organisation's clinical trials registry ICTRP (since 2005).

Specific keywords (including terms related to the care of these patients in the particular emergency setting) were used according to each question at hand, and details of these searches are available in Appendix 2. This process ensured that the recommendations were drafted based on the best available evidence, prioritizing the applicability and relevance of the guidelines to clinical practice in emergency services.

After synthesizing the available evidence from the systematic reviews, the certainty of the evidence was assessed using the GRADE method. The GRADE method offers a transparent approach to evaluate the certainty of the evidence at the outcome level based on eight criteria: risk of bias (methodological flaws), inconsistency (heterogeneity between studies), indirectness (studies conducted in populations other than the initial intended population), imprecision (broad confidence intervals resulting from under-sized studies or studies with small samples), publication bias, magnitude of effect, dose-response effects and confounding bias. After this assessment, the certainty of evidence is divided into 'very low,' 'low,' 'moderate,' or 'high'. (**Table 1**)

When the systematic reviews of the 2022 WHO/PAHO guideline were used, the GRADE certainty of evidence was maintained as originally established, being adapted only when necessary. For the 'de novo' systematic reviews carried out, the aforementioned logic was followed, ensuring that the assessment of the quality of the evidence was consistent and rigorous, allowing for a solid foundation for the guideline's recommendations.

Also, according to GRADE, recommendations can be strong or weak, in favor of or against a specific intervention (**Table 2**).

ADAPTATION PROCESS (GRADE-ADOLOPMENT)

For 7 of the ten priority questions, the GRADE ADOLOPMENT process[12] was used to adopt and/or adapt the recommendations from the WHO/PAHO guideline, using the existing systematic reviews.[10] One of the reasons for this adaptation was the specific context of the WHO guideline, which was drawn up from a Latin American perspective, making it particularly applicable to Brazil. For the other three questions, '*de novo*' systematic reviews were conducted, ensuring a comprehensive and up-to-date analysis of the literature. This procedure ensured that the recommendations were based on the best available evidence.

Table 1. Certainty of evidence according to the GRADE system[11]

Certainty	Definition	Implications
High	There is strong confidence that the actual effect is close to that estimated.	It is unlikely that additional work will change the confidence in the effect estimate.
Moderate	There is moderate confidence in the estimated effect.	Future work could modify the confidence in the effect estimate and may even change the estimate.
Low	Confidence in the effect is limited.	Future work will probably significantly impact our confidence in the effect estimate.
Very low	Confidence in the effect estimate is very limited. There is a significant degree of uncertainty in the findings.	Any estimate of the effect is uncertain.

Table 2. Strength of recommendation according to the GRADE system and its implications for the different target groups[11]

Target groups	"Strong" recommendation	"Weak" recommendation
Managers/ administrators	The recommendation should be adopted as a health policy in most situations.	Substantial debate and stakeholder involvement are needed.
Professionals	The majority of individuals would like the intervention to be indicated, and only a small number would not accept this recommendation.	A large proportion of individuals would like the intervention to be indicated; however, some individuals would not accept this recommendation.
Patients	Most patients should receive the recommended intervention.	The professional must recognise that different choices will be appropriate for each patient to define a decision consistent with their values and preferences.

In drawing up this guideline, the panel paid special attention to the reality of Brazilian emergency services, seeking to ensure the relevance and applicability of the recommendations in the national context. This approach sought to adapt the most effective international practices and ensure their effective implementation in Brazil, taking into account local particularities and the availability of resources. The focus on the WHO/PAHO guideline, which was already geared towards the Latin American reality, made it easier to adapt the recommendations to meet Brazil's specific needs.

USE OF INDIRECT EVIDENCE

The GRADE methodology allows for the use of indirect evidence.[13] Given the lack of specific GRADE recommendations to define 'indirect evidence' or distinguish it from 'direct evidence', we opted to follow the Society for Academic Emergency Medicine (SAEM) definition used in the GRACE guidelines (Guidelines for Reasonable and Appropriate Care in the Emergency Department). 'Direct evidence' would be that which corresponds to each element of the PICO question specific to dengue management. If any element of the published research differed from the PICO question, that study would be considered 'indirect evidence'.

Table 3. Process of adopting and/or adapting recommendations according to the GRADE[12] system

GRADE-ADOLOPMENT Step-by-Step
1. Topics are identified by evaluating existing credible guidelines or evidence syntheses before or after prioritization by a working group involving relevant stakeholders.
2. Clinical questions are prioritized based on local needs and priorities.
3. Existing guidelines are identified through literature searches and other means (or suggested by an entity requiring guidelines, such as a ministry) - they should be relevant, credible, recent, ideally based on GRADE.
4. Recommendations that correspond to the prioritized questions are sought within a guideline.
5. Does a corresponding recommendation exist or not?
6. Identify whether existing systematic reviews need to be updated, e.g., out of date, incomplete, or other outcomes.
7. Does the source guideline have a completed evidence-to-decision framework?
8. If not, one should be developed based on existing information that explains the justification for the recommendation (which should be there if it is considered credible).
9. If evidence-to-decision frameworks are available, the assessments should be reviewed and agreed or disagreed with, indicating reasons for disagreement (e.g. new evidence).
10. An adopted recommendation is developed based on the evaluations of the evidence-to-decision framework.
11. Will the recommendation be similar to the original recommendation?
12. Adopt: the recommendation is the same as the original recommendation.
13. Adapt: the recommendation has been altered to suit the context.
15. Following the above, a new recommendation has been developed.

Question 1

In adult ED patients with suspected or confirmed dengue, should point-of-care ultrasound (POCUS) be used to help identify patients with warning signs? If so, which findings have prognostic value?

Recommendations

1. In adult ED patients with suspected or confirmed dengue, ABRAMEDE suggests the use of POCUS to help identify patients with warning signs.

Reak recommendation; certainty of evidence: very low

Relevant considerations:

- POCUS should be performed by a trained clinician.
- Findings with prognostic value and suggestive of capillary leakage include the presence of cavitary effusion (ascites, pleural effusion, and pericardial effusion) and gallbladder wall thickening (usually > 3 mm). These findings are more commonly present in the disease's critical phase (defervescence) and represent a possible capillary extravasation.
- In patients without high-risk clinical findings detected by history/physical examination and without special conditions, ABRAMEDE does not consider bedside ultrasound mandatory, especially if performing this test would unnecessarily prolong the length of stay in the ED.

Summary of evidence

The systematic review for this guideline found 75 articles, 30 of which were assessed in full text to verify the eligibility criteria by two independent reviewers. Of these 30, 16 were excluded, 9 of which were exclusively in the pediatric population.[14-22] More details on the relevance of indirect evidence from the pediatric population are mentioned later in the text. Other reasons for excluding articles were conference abstracts, Chinese language, study protocols, and non-original studies (e.g., other reviews). After the review, 14 studies evaluating the use of ultrasound in adult patients with suspected or confirmed dengue fever were included. The average age of the patients included in the studies ranged from 21.5 to 49 years, and the countries involved included Pakistan[23-25], Brazil[26], Malaysia[27,28], Indonesia[29], Sri Lanka[30], Mexico[31], India[32-34] and Taiwan.[35]

Of these 14 included studies, only 7 (50%) specifically mentioned that ED patients had been included.[26-28,31,32,34,35] The population of these studies was quite heterogeneous regarding inclusion criteria, ranging from patients with confirmed dengue without warning signs to exclusively hospitalized patients classified as dengue hemorrhagic fever in the old WHO classification. This population heterogeneity precluded any kind of meta-analysis or pooling of the data.

The most studied sonographic findings were gallbladder thickness, ascites, pleural effusion, and pericardial effusion. Among the educational competencies defined by the American College of Emergency Physicians (ACEP)[36], the evaluation of gallbladder wall thickening, especially in the context of cholecystitis, the detection of ascites, pleural effusion and pericardial effusion are part of the basic fundamentals of POCUS performed by the emergency physician. In addition, previous systematic reviews have shown that POCUS performed by a trained operator has good sensitivity and specificity for detecting these findings.[37-39] The key question, however, is whether these findings actually have an impact on the likelihood of a patient with suspected or confirmed dengue fever developing into the severe form of the disease, and this was the focus of the review to answer the guideline's question. It is worth remembering that many of the studies reported the sensitivity of these findings among patients with dengue hemorrhagic fever based on the old WHO classification. This type of analysis suffers from an inherent incorporation bias since the very definition of dengue hemorrhagic fever includes the presence of capillary extravasation.

Evaluation of gallbladder wall thickening has been the most studied ultrasound finding. Most

studies used a cut-off point of 3 mm to define the wall as thickened.[23-25,27,29] One study used the definition of acute acalculous cholecystitis defined by Huffman,[40] considering a cut-off point greater than 3.5-4 mm.[26] No study evaluated the "eyeballing" method, i.e. assessing wall thickness without numerically quantifying it. One study assessed the presence of perivascular fluid but did not report the values in patients with severe dengue.[23] In the studies in which it was possible to reconstruct a 2x2 table and calculate the sensitivity, specificity and likelihood ratios of these findings for the diagnosis of severe dengue, the sensitivity ranged from 9.09% to 100%, the specificity from 13.16% to 78.17%, the positive likelihood ratio from 0.42 to 2.97 and the negative likelihood ratio from 0 to 1.16.

Only four studies reported sufficient data to calculate the ability of the presence of ascites to increase or decrease the likelihood of severe dengue.[23,24,26,29] The positive likelihood ratio ranged from 0.59 to 4.47 (one study reported a specificity of 100% and could not be calculated), while the negative likelihood ratio ranged from zero to 1.64.

Four studies assessed the presence of pleural effusion.[23,24,26,29] The sensitivity of pleural effusion to diagnose severe dengue ranged from 9.09% to 100%, while the specificity ranged from 21.05% to 100%. The positive likelihood ratio ranged from 1 to 1.41, while the negative likelihood ratio ranged from 0 to 1.00.

The assessment of the presence of pericardial effusion was analyzed by two studies.[23,28] One study reported 0 cases of pericardial effusion while the other reported a small number, with a sensitivity of 66.67% and specificity of 92.11% for severe dengue.

One study assessed increased pancreatic size in patients with severe dengue; however, the definition of increased pancreatic size was not described in the study. Assessing pancreatic size is not one of the core competencies of POCUS according to ACEP.[36]

Hepatomegaly was assessed in two studies,[23,26] in one of which there was no definition of what hepatomegaly was[23] and in the other[26] hepatomegaly was defined as the right lobe with a longitudinal diameter from the mid hemiclavicular line to the right portal vein >15cm and the left lobe with a longitudinal diameter from the midline >10cm. The assessment of hepatomegaly is also not part of the core competencies determined by ACEP[36].

Lakshman et al. sought to assess cardiac dysfunction in dengue patients. In this study, cardiac dysfunction was defined if, by the Simpson method, the ejection fraction was less than 50%.[32] Bedside ultrasound had a sensitivity of 28.57% and a specificity of 86.5% for severe dengue. The assessment of cardiac dysfunction by the Simpson method is not part of the core competencies determined by ACEP.[36]

No studies were identified that correlated the presence of B lines on lung ultrasound with severe dengue.

It is worth noting that one of the studies set out to analyze patients with extravasation syndrome exclusively identified by bedside ultrasound and its progression to severe dengue.[28] Chai et al. classified this group as "subclinical" plasma extravasation (i.e. without high-risk elements in the history/physical examination but with some ultrasound findings suggestive of extravasation) and compared this group with those without plasma extravasation on ultrasound. Patients with subclinical extravasation had a higher incidence of progression to dengue with warning signs and severe dengue than those without ultrasound signs of extravasation. This study corroborates the data found in another study,[29] in which 35% of patients who had ascites or pleural effusion at recruitment developed dengue shock syndrome, while 10% of those who did not have extravasation detected by ultrasound developed shock. Although these data suggest that these patients are at greater risk of clinical deterioration, Khurram et al. found no difference in mortality between patients who had ultrasound extravasation and those who did not have ultrasound extravasation.[24]

Regarding the quality of the studies evaluated, the certainty of evidence was considered very low, mainly due to the high risk of bias, inconsistency and imprecision (small samples). Specifically, all the studies were considered to be at high risk of bias according to QUADAS-2,[41] a specific risk of bias tool for systematic reviews that evaluates the domains of patient selection, index test, reference standard and flow/time. No study used a consecutive or random sample of the target population, and many excluded patients inappropriately, probably introducing significant selection bias (for example, most studies included patients who were already hospitalized for other reasons; these patients already had some high-risk factor in the history and/or physical examination), most did not detail who the operator was and their level of training. Only three studies specifically reported that the operator was not a radiologist.[28,29,32] The timing of the ultrasound was also significantly heterogeneous between the studies, which may have introduced an important bias, given that the sensitivity of ultrasound for detecting capillary extravasation can vary throughout the course of the disease (lower in the acute phase, higher during the critical phase). In addition, several of these studies describe the need to fast in order to carry out the test, which is impractical for patients in emergency situations.

With regard to indirect evidence, specifically in the pediatric population, it is worth highlighting the study by Gleeson et al.[16] This study investigated the potential of bedside ultrasound performed by emergency clinicians to predict the clinical deterioration of children with suspected dengue being seen in an emergency unit in the first few days of illness (average of 3.6 days). Patients who were discharged after a clinician's assessment and had an enlarged gallbladder (> 3 mm) had a higher risk of returning for care than those without a thickened wall (67% vs 17%; odds ratio [OR] 11.1, 95% CI 3.4 to 36.6). Other findings, such as ascites, pleural effusion and pericardial effusion, were less common and were not associated with a higher risk of returning. Another finding reported in a very small number of patients was the presence of B-lines, also without an association in relation to returning to the ED. However, when the authors considered any finding on ultrasound, patients with any abnormality on ultrasound were more likely to be admitted (62.2% *versus* 19.5%).[16]

Benefits

The use of POCUS seems to help in identifying warning signs and can help stratify the risk of these patients. This test, when carried out by a trained operator, has greater sensitivity than physical examination in identifying cavitary effusions, which improves the emergency physician's ability to risk stratify these patients. In addition to cavitary effusions, gallbladder thickening seems to be associated with an increased risk of developing severe forms, but it is not clear from the literature whether this would be a finding that would change management independently of other clinical findings. Although ultrasound is useful in identifying ascites, pleural effusion, pericardial effusion and gallbladder thickening, it is not clear that performing it systematically in all adult patients with suspected or confirmed dengue does have an impact on clinical outcomes. Only one study has evaluated the impact of the "subclinical" syndrome of capillary leakage (i.e. negative history and clinical examination but presence of suggestive findings on ultrasound) and showed an association with a higher risk of clinical deterioration; however, this was a very small study with many methodological limitations.[28] This fragility of the evidence is corroborated by the study by Khurram et al., which found no difference in mortality between patients who had ultrasound leakage and those who did not have ultrasound leakage.[24]

Harms and burden

POCUS is not a widely available resource in all EDs, which could lead to an increase in the number of formal tests performed by a radiologist, potentially increasing the ED length of stay without offering a clear benefit. In addition, there

is the possibility of identifying incidental findings that are not related to the condition in question, which can complicate diagnosis and patient management.

Another important aspect is the fact that ultrasound is a test that depends significantly on the skill of the operator. Considering that the majority of clinicians working in EDs in Brazil have no formal training in Emergency Medicine and that a large proportion of these professionals have no specific training in bedside ultrasound, implementing this recommendation can be challenging.

Decision criteria and additional considerations

Although the evidence for the systematic use of POCUS for all adult patients with suspected or confirmed dengue fever in the ED is weak, the panel considered that this test can aid in the risk stratification of these patients provided it is performed by a trained clinician and does not prolong the length of stay in the ED unnecessarily. Current evidence shows that there is a significant knowledge gap,[42] but also that this gap can be filled with training.[43] Several questions about training need to be addressed. Who will provide it? At what level(s) of trainees' experience should training take place? Will medical schools, residency programs in Emergency Medicine or accreditation organizations adopt it? How much will it cost, and who will pay for it? These questions have yet to be fully defined.

Equity in healthcare provision

As training issues are resolved and more devices are present in Brazil's EDs, performing ultrasound at the bedside could improve equity for patients with this and other diseases. This way, emergency physicians will be able to risk stratify more accurately. In addition, with the use of a bedside examination, especially with handheld devices, the prospect is that the time it takes to provide care will decrease and help in decision-making, improving the flow of patient care in the ED.

Conclusions and future research needs

Although the evidence is not robust for the systematic use of POCUS in these patients, its high sensitivity in identifying findings considered prognostic (e.g. cavitary effusions) seems to justify a recommendation for its use in the ED. It is unclear whether these findings actually increase the likelihood of severe dengue once they are found, and more studies on the use of ultrasound in adult patients, especially at the beginning of the illness, need to be carried out. In order to implement the use of POCUS in these patients, Brazilian authors recently proposed the E-FASD (Extended Focused Assessment Sonography in Dengue) protocol with the systematic performance of pulmonary, cardiac and abdominal windows (including evaluation of the gallbladder).[44]

Question 2

In adult ED patients with suspected or confirmed dengue, what basic clinical findings and laboratory tests should be used to identify high-risk patients (i.e. at risk of progressing to severe disease)?

Recommendations

2a. In adult ED patients with suspected or confirmed dengue, ABRAMEDE recommends that all of the following clinical findings should be actively sought to identify high-risk patients:

Strong recommendation; level of evidence: low to high depending on the prognostic factor assessed

- Signs of shock (altered mental status, cold and poorly perfused extremities, increased capillary refill time, increased shock index, tachycardia, hypotension, low pulse pressure and oliguria).
- Respiratory failure.
- Abdominal pain that is progressively worse until it becomes continuous or of strong intensity despite simple analgesia.
- Persistent vomiting (3 or more episodes in 1 hour or four episodes in 6 hours).

- Sudden onset hepatomegaly, whether identified clinically (> 2 cm below the costal margin) or by POCUS.
- Fluid accumulation (ascites, pleural effusion and/or pericardial effusion), whether identified clinically or by POCUS.
- Mucosal bleeding, including gingivorrhagia, epistaxis, vaginal bleeding not associated with menstruation and hematuria.
  - ✓ Relevant considerations: the panel considered that the routine use of the tourniquet test to look for induced skin bleeding is not considered mandatory in the initial assessment of these patients.

2b. In adult ED patients with suspected or confirmed dengue, the recommendations for additional tests vary according to the clinical situation.

- In patients with one or more high-risk clinical findings or with special conditions, ABRAMEDE recommends that a hematocrit be requested during their stay in the ED.

Strong recommendation; level of evidence: high

- Relevant considerations: "special conditions" include extremes of age (< 2 years and > 75 years), pregnant women and/or the presence of comorbidities (uncontrolled hypertension or other serious cardiovascular diseases, uncontrolled diabetes mellitus, chronic obstructive pulmonary disease (COPD), asthma, obesity, chronic hematological diseases, chronic kidney disease, liver diseases and immunosuppression for any cause).
- In patients with one or more high-risk clinical findings or with special conditions, ABRAMEDE suggests performing a complete blood count with platelets, coagulogram, transaminases, serum albumin and renal function to help stratify risk.

Weak recommendation; level of evidence: low to high depending on the prognostic factor assessed

- In patients without any high-risk clinical findings, without special conditions and with medical-social conditions for brief or immediate hospital discharge, ABRAMEDE suggests not performing additional tests during their stay in the ED.

Weak recommendation; level of evidence: very low).

Summary of evidence

The systematic review carried out by PAHO/WHO analyzed 217 studies involving 237,191 patients diagnosed with dengue, with the aim of investigating the association between various prognostic factors and the development of severe forms of the disease.[10] From this review, it was identified that 21 factors had predictive potential. Among these, 12 factors had a moderate to high level of evidence, including low pulse pressure, hypotension, abdominal pain, mental confusion, mucous membrane bleeding, fluid accumulation, respiratory difficulty, liver enlargement, low platelet count, elevated transaminases, increased hematocrit and vomiting. As for the other factors, the certainty of evidence was low, covering acute renal failure, delayed capillary refill time, pregnancy, microscopic hematuria, coagulopathies, enlarged spleen, high fever, positive loop test and diarrhea. The PAHO/WHO guideline considered that only the 12 prognostic factors with a moderate to high certainty of evidence would result in important benefits if they were actively pursued. However, the ABRAMEDE panel considered that other variables associated with worse outcomes should also be considered as high-risk findings, even if the level of evidence is lower. For example, prolonged capillary refill time is a sign of shock that has been widely validated in the literature, although most of the studies are not on dengue patients[45]. In addition, the panel considered that the prognostic factors should be named "high-risk variables" (a term widely used in Emergency Medicine literature to identify patients at high risk of unfavorable

short-term evolution). These variables are separated into "clinical findings", which should be identified in the initial assessment of any patient seen in the ED with suspected or confirmed dengue, and "additional tests", which should only be used in patients who have any high-risk clinical findings and/or special clinical conditions in the initial assessment.

The panel considered that the tourniquet test is not mandatory in the initial assessment of these patients, taking into account that the effect estimate found in the systematic review showed a weak association with progression to severe dengue, including a confidence interval crossing unity (i.e. without a statistically significant difference between those who had a positive tourniquet test and those with a negative tourniquet test). In addition, making this assessment mandatory could unnecessarily prolong the length of stay in the ED. Even so, even if this were done, patients with skin bleeding (petechiae or positive test [if this test is done]) who have normal exams and do not develop high-risk clinical findings during hospital observation would not need to be admitted.

Of the findings considered high risk by ABRAMEDE, the strength of the association with the odds of progressing to severe dengue is expressed as an odds ratio with the confidence interval in **Table 4**.

Benefits

Although there are no studies that directly evaluate the impact of using different prognostic factors on clinical outcomes, the panel recognised the benefits of improving the ability to identify high-risk patients. This identification can be carried out without the need for complex tests based solely on history and physical examination. In places with access to bedside ultrasound and with competent operators, this tool could be added to the traditional clinical examination in an attempt to identify high-risk findings, but it is not considered mandatory in the initial screening of these patients. There are interventions available that can considerably improve the prognosis of these patients (e.g. parenteral hydration). Additionally, the identification of these high-risk variables through clinical history and physical examination allows the emergency physician to make more informed decisions about patient management, including options such as hospitalization, observation for a short period, and discharge with an indication of a short return, among other hospital disposition strategies.

Harms and burden

Clinical history and physical examination are fundamental components of medical assessment, which, in general, cause no harm to the patient, and represent a safe and non-invasive approach to identifying high-risk clinical findings. However, for patients who present with these findings and who consequently require laboratory tests, ultrasound or radiography, there may be minimal discomfort associated with these procedures. In addition, such tests can reveal incidental findings that are unrelated to the initially suspected clinical picture, which can introduce additional complexity to the diagnosis and decision-making and, in some cases, can confuse patient management.

Decision criteria and additional considerations

The panel emphasizes the importance of clearly distinguishing the active search for high-risk clinical findings, which do not require complex tests and can be identified through history and physical examination in any ED, from basic additional tests. This distinction is intended to avoid over-indication of these tests by emergency physicians and other professionals who will be using this guideline. In addition, the panel recognises the relevance of identifying high-risk factors to assist in decision-making about the appropriate hospital disposition, whether for observation, hospitalization or discharge and in the implementation of early interventions, such as parenteral hydration.

Equity in healthcare provision

Most of the prognostic factors identified are easily applicable in any context since they are obtained through clinical history and physical examination, procedures that can be carried out in any location. Thus, there is unlikely to be a negative impact on equity. However, ABRAMEDE stresses that additional tests should only be carried out on patients with any high-risk clinical findings. The inclusion of indicators such as a progressive increase in hematocrit, thrombocytopenia, an increase in transaminases and acute renal failure, which require specific laboratory tests, could reduce equity since not all emergency services have these tests available. Although bedside ultrasound is a non-invasive procedure with potential prognostic/predictive value, its availability is still limited in most emergency services in Brazil.

Conclusions and future research needs

It is essential to avoid over-indicating laboratory tests in patients who do not present high-risk clinical findings, with a view to both optimizing the use of resources and reducing unnecessary interventions. There is an urgent need for studies that clarify the most effective screening mechanisms in epidemic scenarios, with the aim of developing a score or stratification rules that have a high sensitivity for identifying patients in need of immediate attention. Despite the identification of risk factors associated with more serious illness, the lack of proof of the effectiveness of these criteria as a triage tool highlights a gap in knowledge that needs to be filled. In addition, it is important to consider that even though certain prognostic factors may indicate a greater risk, their absence does not guarantee patient safety since none are

Table 4. Prognostic factors and strength of association with severe dengue[10]

Prognostic factor	Effect estimate (OR, 95% CI)	Certainty of evidence
Clinical findings		
Altered mental status (33 studies, 76,881 patients)	5.23 (3.45-7.93)	High
Bleeding (59 studies, 18,469 patients)	5.21 (3.53-7.69)	High
Fluid accumulation (54 studies, 26,241 patients)	5.04 (3.56-7.14)	High
Difficulty breathing (12 studies, 25,771 patients)	3.93 (2.90-6.42)	High
Hepatomegaly (62 studies, 25,989 patients)	3.14 (2.38-4.15)	High
Abdominal pain (87 studies, 85,769 patients)	2.02 (1.74-2.35)	High
Mucosal bleeding (50 studies, 24,661 patients)	1.96 (1.47-2.69)	High
Vomiting (56 studies, 72,312 patients)	1.74 (1.48-2.05)	High
Low pulse pressure (6 studies, 5,096 patients)	7.12 (3.02-16.76)	Moderate
Hypotension (19 studies, 7,463 patients)	5.38 (3.31-8.75)	Moderate
Prolonged capillary refill time (3 studies, 210 patients)	4.96 (1.72-14.32)	Low
Pregnancy (1 study)	3.38 (2.10-5.42)	Low
Microscopic hematuria (3 studies, 1,831 patients)	3.12 (1.23-7.90)	Low
Positive tourniquet test (32 studies, 16,133 patients)	1.48 (0.99-2.20)	Low
Petechiae or ecchymoses (31 studies, 9,663 patients)	1.21 (0.96-1.52)	Low
Additional tests		
Increase in hematocrit (45 studies, 17,462 patients)	2.30 (1.74-3.05)	High
Thrombocytopenia (62 studies, 50,586 patients)	3.02 (2.45-3.73)	High
Elevated transaminases (39 studies, 18,579 patients)	2.55 (1.78-3.64)	High
Acute renal failure (8 studies, 4,348 patients)	6.73 (1.66-27.20)	Low

OR, odds ratio. CI, confidence interval.

sensitive enough to completely rule out the risk of deterioration. This observation highlights the importance of prudence when interpreting clinical data and managing patients.

Question 3

In adult ED patients with suspected or confirmed dengue, what clinical findings and basic tests (laboratory, bedside radiography and ultrasound) should be used to identify patients who require hospitalization?

Recommendations

3. In adult ED patients with suspected or confirmed dengue, ABRAMEDE suggests that the following criteria be used to define hospitalization:

Weak recommendation; level of evidence: low to high depending on the prognostic factor assessed

- Presence of 1 or more high-risk clinical findings.
- In patients who have undergone additional tests, the presence of findings that imply the need for parenteral hydration or other therapy that can only be carried out in the hospital. These findings include:
    - Increased hematocrit (defined as an increase in hematocrit equal to or greater than 20 per cent above the average for age, sex and population).[46]
    - ✓ Presence of ascites, pleural effusion or pericardial effusion.
    - ✓ Significant thrombocytopenia (<50,000/uL).
    - ✓ Significant increase in transaminases (≥ 1000/uL).
    - ✓ Acute renal failure (as defined by the KDIGO guidelines):[47]
        - Increase in serum creatinine ≥ 0.3 mg/dL in 48 hours, or
        - Increase in serum creatinine by 1.5x baseline creatinine within the last seven days or
        - Diuresis < 0.5 ml/kg/h for 6 hours.
- Inability to maintain adequate oral hydration at home.

Relevant considerations:

- Considering the robust literature showing an association between prolonged ED length of stay and worse clinical outcomes, Once hospital admission has been decided, it should take place in ward beds or intensive care beds, minimizing the length of stay in the ED as much as possible.
- According to Federal Council of Medicine Resolution No. 2.077/2014, the maximum length of stay for patients in Urgent and Emergency Hospital Services in Brazil is up to 24 hours, after which they must be discharged, admitted or transferred[49]
- In extreme situations of epidemics and hospital overcrowding, it is reasonable to use these criteria to select patients for out-of-hospital health units, such as hydration tents, provided that they have the structural and technical conditions to monitor and treat patients.[50,51]

Summary of evidence

No studies were found on patients with suspected or confirmed dengue fever that evaluated the impact of using different variables or combinations of variables to select patients requiring hospitalization on clinically relevant outcomes.[10] Therefore, the ABRAMEDE panel, like the WHO panel, considered it reasonable to use prognostic factors among the criteria for hospital admission, even though there is no robust evidence supporting this strategy. The strength of the association between prognostic factors and the risk of clinical deterioration was described in the previous question of this guideline (**Table 4**).

Benefits

The inclusion of high-risk clinical findings in the criteria for hospital admission reflects the understanding that such patients are likely to benefit from intravenous hydration and closer monitoring

to detect any clinical or laboratory deterioration. Generally, the presence of these findings indicates the onset of the critical phase of the disease or represents the very manifestation of this critical phase.

Harms and burden

Some patients identified with high-risk clinical findings may not progress to severe forms of dengue. In these cases, hospitalization can lead to harm related to the hospital environment itself, including unnecessary interventions, excessive collection of tests, adverse events related to health care, increased risk of infections, possibility of delirium and risk of falls (especially in older patients), among other problems.

Decision criteria and additional considerations

The inclusion of high-risk clinical findings and certain laboratory results that indicate the need for parenteral hydration or other hospital interventions as criteria for hospitalization is based on the premise that such indicators suggest a greater risk of clinical deterioration in the short term and, therefore, require monitoring in the hospital environment. However, it is crucial to take into account the possible scenarios that can arise, especially during epidemics, where this approach can result in overcrowding of EDs and hospitals. In view of this, it becomes reasonable to consider, in these circumstances, the management of patients with high-risk clinical findings but without signs of marked severity in less complex units, such as parenteral hydration tents with minimal monitoring. Some observational studies carried out in Rio de Janeiro describing hydration tents during epidemics show morbidity and mortality rates close to 0%.[50,51] This strategy seeks to balance the need for adequate care with the optimisation of hospital care capacity, minimizing the risk of overcrowding and ensuring that resources are directed effectively.

In the spectrum of patients presenting with one or more high-risk clinical findings, certain variables are more obvious when making the decision to admit them to the hospital, such as the presence of hypotension, increased capillary refill time and changes in mental status, all of which are indicative of shock. On the other hand, the decision to hospitalize patients who present with symptoms such as severe abdominal pain, vomiting and slight hemoconcentration detected in the blood count may not be so straightforward. However, it is recognised that these patients have a high risk of clinical deterioration if they do not receive parenteral hydration and follow-up in a hospital environment to monitor their progress.

Equity in healthcare provision

It is essential to recognise that most prognostic factors can be identified through clinical history and physical examination, methods that are accessible in any emergency care setting. This approach, which does not require material resources beyond the expertise of a qualified emergency physician, is a positive indication of equity, allowing the identification of patients who require hospitalization regardless of the context. However, the need for additional tests, such as blood tests or ultrasound, for decision-making in specific cases introduces a potential limitation to equity. The availability of these resources varies significantly between different places of care, which can, to some extent, reduce equity in access to healthcare. Emergency and urgent care services that do not have easy access to these tests may face additional challenges in the proper assessment and management of patients, especially in situations where such tests can provide crucial information for decision-making. Thus, while the use of clinical findings as the primary means of identifying patients requiring hospitalization reflects an equitable practice, the reliance on specific tests, which are not universally available, highlights the need for strategies that expand accessibility to these critical resources to ensure health equity.

Conclusions and future research needs

The importance of avoiding ED overcrowding is a crucial aspect, guiding the avoidance of hospital

admission for patients who do not meet the hospitalization criteria. However, it is essential to recognise that the decision not to admit a patient does not exclude the possibility that they may need to be hospitalized at a later date. This underlines the need for careful monitoring of patients who are discharged to primary care units or through alternative strategies such as telemedicine, ensuring a continuous review of their state of health. It also highlights the need for future research into the best strategy for defining hospitalization. The approach proposed by ABRAMEDE and those proposed by the Ministry of Health and WHO have gaps in terms of robust evidence, highlighting the importance of studies that seek to determine the superiority of one strategy over the other. This effort is vital for optimizing patient care, minimizing the risk of ED overcrowding and ensuring that hospitalization decisions are based on solid clinical criteria and scientific evidence.

Question 4

In adult ED patients with suspected or confirmed dengue, what clinical findings and basic tests should be used to identify patients who require hospitalization in an intensive care unit (ICU)?

Recommendations

4. In adult ED patients with suspected or confirmed dengue, ABRAMEDE recommends that patients with clinical instability, defined as the need for support for organ dysfunctions and intensive monitoring, should be admitted to an ICU bed.

Strong recommendation; statement of good practice

Relevant considerations:

- Basic clinical or laboratory findings should not be used in isolation to define the need for ICU admission.
- The indication for ICU admission can be dynamic and varies according to the initial assessment and management of the patient in the ED. However, once clinical instability and the need for intensive monitoring have been established, it is recommended that the emergency physician list the patient for an ICU bed.
- According to Federal Council of Medicine resolution No. 2,156/2016, ICU admissions must take into account the medical services available at the institution, prioritization according to the patient's condition, bed availability and the potential benefit to the patient from therapeutic interventions and prognoses.

Summary of evidence

No studies were found in patients with suspected or confirmed dengue that evaluated the impact of using different variables or combinations of variables to select patients who require admission to an ICU bed.[10] Although there are no specific studies that establish ICU admission criteria for patients with suspected or confirmed dengue, the ABRAMEDE panel proposes that these criteria should be based on the principle that patients requiring support for critical organ dysfunction and intensive surveillance should be eligible for ICU admission. This would include patients with severe forms of dengue, such as those in shock who do not respond to initial interventions in the ED, patients with acute respiratory failure, need for mechanical ventilatory support, significant coagulation disorders and severe bleeding, among other conditions that require intensive care similar to that required for other serious infections.

Benefits

This more comprehensive approach offers the main advantage of aligning the ICU admission criteria for cases of severe dengue with those applied to other serious infections, eliminating the need for a specific dengue protocol that the emergency physician would need to learn and apply.

Harms and burden

The main disadvantage of this approach is that, during epidemics, the increase in the number of

patients with clinical instability can lead to an excessive demand for ICU beds, potentially overloading the available hospital resources. However, it is important to note that although most EDs have "critical care rooms" equipped for continuous monitoring, the quality of care for critically ill patients can be compromised by the lack of appropriate equipment and a shortage of qualified staff. It is not uncommon, for example, for EDs to lack an adequate ratio of nursing technicians or nurses per patient, directly affecting the quality of ED-based critical care.

Decision criteria and additional considerations

ABRAMEDE's recommendation reinforces the notion that establishing more detailed criteria for ICU admission should take into account various factors, as recommended by the Federal Council of Medicine resolution. These factors include the medical resources available at the institution, prioritization based on the patient's clinical condition, the availability of ICU beds and the potential benefit of therapeutic interventions and prognoses for the patient.

Equity in healthcare provision

The recommendation to refer patients to the ICU faces the challenge of limited bed availability, reducing equity in access to this level of care. This limitation can result in the need to transfer patients to other institutions, adding complexity to the treatment process and potentially delaying the achievement of adequate critical care.

Conclusions and future research needs

Future research is essential to determine whether, among patients with severe dengue, there is a subgroup that responds promptly to initial therapies and could benefit from care in an intermediate unit, thus avoiding the need for immediate admission to the ICU. In addition, it is necessary to explore whether more specific variables or a combination of them, can establish more precise criteria for ICU admission, allowing for a more targeted approach and potentially increasing the efficiency and effectiveness of the use of critical hospital resources.

Question 5

In adult ED patients with suspected or confirmed dengue who have high-risk clinical findings, should parenteral hydration be indicated?

Recommendations

5. In adult ED patients with suspected or confirmed dengue fever who have high-risk clinical findings, ABRAMEDE recommends starting parenteral hydration.

Strong recommendation; level of evidence: very low

- Relevant considerations: parsimony is required in the administration of intravenous fluids in patients with conditions that predispose to volume overload, such as those with heart failure and/or chronic kidney disease.

Summary of evidence

The WHO systematic review did not identify any randomized or observational studies in which the indication for parenteral hydration was compared to conservative management (without parenteral hydration) for dengue patients presenting with warning signs.[10] In the absence of studies with a control group, the level of evidence is inevitably very low, and the existing evidence comes from studies that provided parenteral hydration to all patients, and the rate of outcomes such as mortality was low. For example, in a study during the 2008 dengue epidemic in Rio de Janeiro, 2,594 adults were treated in hydration tents, of whom 365 received parenteral hydration due to the presence of warning signs.[51] Notably, there were no deaths among these patients. This study highlights that the use of parenteral hydration in patients with warning signs in health facilities of less complexity than the ED was linked to an extremely low rate of mortality. In addition to low mortality, two other

studies found by the systematic review showed that in cohorts where parenteral hydration was implemented, the incidence of shock was 2-5%.[50-52]

Despite the potential benefit of parenteral hydration, one study assessed the impact of parenteral hydration on the risk of respiratory failure due to volume overload and showed that there is an association with an increased risk of respiratory failure due to volume overload (hazard ratio [HR] = 2.90, 95% CI 1.37-6.12)[53]. This risk is probably higher in patients with predisposing conditions such as heart failure and chronic kidney disease.

Benefits

The benefits of parenteral hydration in dengue patients with high-risk clinical findings include a likely reduction in the risk of progression to more severe stages of the disease. In addition, parenteral hydration is a low-cost intervention and is widely available in EDs. The study carried out in hydration tents during the dengue epidemic in Rio de Janeiro provides indirect evidence that this practice may be linked to a reduced rate of morbidity and mortality among these patients. This finding reinforces the value of parenteral hydration not only as an effective measure to combat the progression of dengue but also as an affordable and practical strategy to improve clinical outcomes in patients with high-risk clinical findings of the disease.

Harms and burden

One of the possible harms of parenteral hydration, particularly when applied aggressively and without due precautions in higher-risk patients, is volume overload, resulting in pulmonary edema and subsequent respiratory failure. One way to mitigate this risk, especially in patients with a greater predisposition to overload, such as those with heart failure and chronic kidney disease, is to assess fluid tolerance.[54] This can be done, for example, using bedside ultrasound or through more frequent clinical reassessments, even without the use of ultrasound, to carefully monitor the patient's condition and adjust hydration therapy as necessary.

Decision criteria and additional considerations

The decision-making criteria highlight that parenteral hydration is a simple and cost-effective intervention, which tends to be beneficial for patients with a suspected or confirmed diagnosis of dengue presenting with high-risk clinical findings. It is important to note, however, that determining the volume of fluids to be administered to patients remains a matter of debate and has not been explored in detail in this discussion. In addition, it is likely that all emergency care facilities in Brazil have the necessary resources to implement this intervention, which facilitates its application in a broad healthcare context.

Equity in healthcare provision

The panel recognised that since parenteral hydration is a widely available intervention in EDs and can reduce the need for more complex and costly procedures (avoiding, for example, progression to shock and the subsequent need for ICU admission), this practice probably contributes positively to health equity at the population level.

Conclusions and future research needs

Although an ideal study would compare parenteral hydration versus control without parenteral hydration in patients with high-risk clinical findings, the very low rates of serious adverse events in the cohorts undergoing parenteral hydration make it unlikely that future research will be carried out in this direction. Thus, the focus of studies could turn to determine the most effective approach to parenteral hydration in these high-risk patients, such as investigating the ideal amount of volume, the time of administration, and gradual reduction strategies, among other aspects. Currently, the recommendations provided by the Ministry of Health and the WHO are based on empirical practices rather than solid evidence.

Question 6

In adult ED patients with suspected or confirmed dengue fever who receive parenteral hydration, should replacement with crystalloids or colloids be started?

Recommendations

6a. In adult ED patients with suspected or confirmed dengue who receive initial parenteral hydration, ABRAMEDE recommends using crystalloids

Strong recommendation; level of evidence: low to high depending on the outcome assessed

6b. In adult ED patients with suspected or confirmed dengue who receive parenteral hydration with crystalloids, ABRAMEDE suggests using ringer lactate.

Weak recommendation; level of evidence: low

- Relevant considerations: In places where ringer lactate is not available, normal saline (NaCl 0.9%) is a reasonable alternative.

Summary of evidence

Four randomized clinical trials were identified that compared the use of crystalloids and colloids in 694 patients with dengue shock or severe dengue.[55-58] In addition, indirect evidence from a Cochrane systematic review was included from 69 randomized studies that compared crystalloids with colloids for resuscitation of patients with shock from other causes.[59]

The use of crystalloids does not appear to have an impact on mortality (no events were observed in either group in the four clinical trials evaluated, and indirect evidence suggests a lack of significant differences), the risk of recurrent or treatment-resistant shock (relative risk [RR] = 1.06; 95% CI: 0.82 to 1.37; moderate certainty of evidence), or volume overload (RR = 1.01; 95% CI: 0.76 to 1.34; moderate certainty). However, the use of crystalloids reduces the risk of infusion-related or allergic reactions (RR = 0.09; 95% CI: 0.01 to 0.64; risk difference [RD] = -3.7%; 95% CI: -4.1 to -1.5%; high certainty) and could reduce the need for renal replacement therapy (RD = -24%; 95% CI: -11 to -39; low certainty).[10]

In addition to comparing crystalloids with colloids, there are studies that evaluate the different types of crystalloids against each other. A meta-analysis carried out by Zampieri et al., published in 2024, covered six randomized clinical trials involving a total of 34,685 critically ill patients (not specifically including suspected or confirmed dengue cases). Using a Bayesian meta-analysis, the use of balanced solutions such as ringer lactate was associated with a high probability of reducing mortality (when compared to unbalanced solutions such as normal saline). On the other hand, in patients with head trauma and/or other neurocritical conditions, an association of saline with a lower mortality rate was observed. The certainty of evidence for these estimates was considered moderate in the original meta-analysis, but we have downgraded them as indirect evidence.[60]

Benefits

Despite probably not having a significant impact on mortality, crystalloids offer a number of benefits, including a lower risk of needing renal replacement therapy, a reduced incidence of allergic or infusion-related reactions, and lower cost. According to data collected by the WHO, cost analysis of the different fluids indicates that crystalloids, such as saline and ringer lactate solution, are less expensive, costing US$ 0.001 per milliliter, while colloids such as dextran and polygeline, cost US$ 0.01 per millilitre.[10]

Harms and burden

Regarding the comparison between crystalloids and colloids, the panel did not identify any harms associated with the use of crystalloids.

Decision criteria and additional considerations

The decision criteria for preferring crystalloids were based on their widespread acceptance, the potential

benefit in relation to secondary outcomes, such as the need for renal replacement therapy and the occurrence of allergic reactions, as well as their low cost. The WHO and Ministry of Health guidelines suggest the use of saline solution (NaCl 0.9%). However, the four existing clinical trials that compared crystalloids versus colloids in dengue used ringer lactate.[55-58] In studies with non-dengue patients, ringer lactate was preferable to normal saline in practically all populations except patients with severe TBI. Also, excessive use of saline is associated with an increased risk of developing hyperchloremic acidosis.[61] That said, both options are reasonable, but the ABRAMEDE panel suggests that ringer lactate should be the first choice crystalloid. In the absence of ringer lactate, however, the use of normal saline is reasonable.

Equity in healthcare provision

The limited availability of colloids in some emergency units reinforces the choice of crystalloids since they are widely available, thus promoting equity in treatment.

Conclusions and future research needs

There is an urgent need for new research that explores the optimal volume of crystalloids, the speed of infusion, as well as best practices for progressively decreasing therapy, among other relevant issues. The current guidelines from the Ministry of Health and the WHO are based on empirical conventions and lack robust evidence base.

Question 7

In adult ED patients with suspected or confirmed dengue with thrombocytopenia but without active bleeding, should prophylactic transfusion of blood components (platelet concentrate or fresh frozen plasma) be indicated? If so, at what platelet cut-off value?

Recommendations

7. In adult ED patients with suspected or confirmed dengue with thrombocytopenia but without active bleeding, ABRAMEDE suggests against routinely transfusing platelets and/or fresh frozen plasma.

Weak recommendation; level of evidence: very low

Relevant considerations:

- This recommendation does not apply to patients with active bleeding who may benefit from transfusion.
- In patients with platelets ≤ 10,000/mm^3, it is reasonable to individualize the decision on prophylactic transfusion considering the recommendations of other guidelines with higher-risk populations (e.g. chemotherapy-induced thrombocytopenia).[62]

Summary of evidence

Three randomized clinical trials[63-65] evaluating the effects of blood component transfusion in 565 patients with dengue and thrombocytopenia were identified, and one observational study[66] contributed additional data. Some studies included patients with ≤ 20,000/mm^3, while others used higher cut-off points such as < 40,000/mm^3. In other words, they included patients with severe thrombocytopenia.

Analysis of this evidence shows that the impact of prophylactic platelet transfusion on both mortality (OR = 5.36; 95% CI: 0.25 to 115; RD = 4.7%; 95% CI: -0.9 to 55.9) and the incidence of shock (OR = 0.71; 95% CI: 0.14 to 3.65; RD = -1.6%; 95% CI: -4.8-12.2) remains uncertain, as evidenced by the extremely wide confidence interval. Platelet transfusion showed a small but not statistically significant reduction in the risk of major bleeding (OR = 0.58; 95% CI: 0.18-1.90; RD = -1.3%; 95% CI: -2.5 to 2.6), but appears to significantly increase the risk of adverse events (OR = 8.23; 95% CI: 1.84 to 36.8; RD = 2.5%; 95% CI: 0.3 to 11.2).[10]

The observational study carried out in Singapore, which compared patients with severe thrombocytopenia (< 20,000/mm^3) who did and did not receive prophylactic platelets, showed that those who were transfused stayed in the hospital an average of 1 day longer, with no difference in clinical outcomes such as mortality or major bleeding.[66]

Benefits

The available evidence does not support the existence of a benefit in transfusing platelets or plasma prophylactically to patients with thrombocytopenia who do not have active bleeding.

Harms and burden

The main problem with prophylactic transfusion is the higher incidence of transfusion-related adverse events, as well as the fact that it is not a widely accessible intervention, given the frequent shortage of platelets and plasma in blood banks. The indiscriminate preventive use of these blood components could exacerbate stock shortages, compromising care for other prevalent and life-threatening conditions that require urgent transfusions (e.g. severe trauma patients). In addition, its routine use seems to be associated with an increase in hospital length of stay.

Decision criteria and additional considerations

The panel took into account the uncertainty about the benefits of transfusion and the evidence pointing to an increase in adverse events as decisive factors, together with the limitation of the health system in providing the necessary structure to carry out prophylactic transfusions. Even if there is a minimal benefit, the number of patients who would need to be treated to prevent a case would probably be very high, resulting in several individuals being exposed to risks arising from transfusions and an unnecessarily prolonged stay in EDs.

Equity in healthcare provision

The limited availability of platelet and plasma transfusions in emergency care services may compromise equity in access to these interventions.

Conclusions and future research needs

The accuracy of the effect measures is probably limited by the small number of patients studied, indicating that more definitive answers could be obtained through larger clinical trials. Prophylactic platelet transfusion does not seem to have a clear benefit, except in situations of severe thrombocytopenia due to hyperproliferation in the context of cancer[62,67] or thrombocytopenia requiring invasive procedures.[68] With this in mind, future research could be more fruitful by focusing on blood component transfusion strategies in patients who are actively bleeding, covering not only platelet transfusion but also red blood cell concentrate, plasma, fibrinogen and/or cryoprecipitate.

Question 8

In adult ED patients with suspected or confirmed dengue, what pharmacological interventions can be indicated to treat the symptoms?

Recommendations

8. In adult ED patients with suspected or confirmed dengue, ABRAMEDE suggests the use of dipyrone and/or paracetamol to control symptoms.

Weak recommendation; very low to low level of evidence depending on the medication

Relevant considerations:

- In patients without adequate symptom control, it is important to consider the maximum doses of both drugs before considering alternative medications.
  - ✓ Maximum paracetamol dose: 4 g/day.
  - ✓ Maximum dose of dipyrone: 4 to 6 g/day.[69]
- In patients without adequate symptom control despite the maximum doses of the suggested medications, it is reasonable to consider the use of non-steroidal anti-inflammatory drugs
- (NSAIDs).

Summary of evidence

We analyzed five non-randomized studies on the safety of NSAIDs in 2,692 dengue patients and added information from 18 studies with 3,361 people treated for musculoskeletal injuries. Regarding paracetamol, two randomized and four

non-randomized studies were included, totalling 3,220 dengue patients. As for dipyrone, one randomized and four non-randomized studies looked at its safety in 1,199 patients with dengue, as well as data on its safe use in 3,716 patients with other conditions. The certainty of evidence on the effects of NSAIDs, paracetamol and dipyrone was considered very low due to the risk of bias in the studies analyzed, imprecision (small studies) and inconsistency between some studies.

Non-steroidal anti-inflammatory drugs

There is uncertainty about the effect of NSAIDs in increasing the risk of bleeding in patients with dengue. A non-randomized study of 683 dengue patients, 154 of whom had bleeding of unspecified clinical relevance, showed an adjusted OR of 0.86 (95% CI: 0.51-0.97).[70] Another four non-randomized studies, covering 2,054 dengue patients and 368 cases of bleeding without correction for confounding factors, had mixed results: two of them pointed to an increase in the incidence of bleeding in patients treated with NSAIDs,[71,72], while the other two did not identify an increase in incidence.[73,74] In studies of dengue patients, there is also uncertainty about the effect of NSAIDs on the incidence of abdominal pain and liver damage. In studies of acute pain treatment in other populations, the use of NSAIDs seems to be associated with a higher risk of nausea and abdominal pain.[75]

Paracetamol

There is uncertainty about the effect of paracetamol on the risk of bleeding in dengue patients: two randomized studies observed a total of 2 gastrointestinal bleeding events and three minor bleeding events in 104 patients randomized to paracetamol, and no events in 63 patients randomized to the control group (placebo or dipyrone), respectively.[76,77] A non-randomized study, which included 729 patients with dengue fever and 86 bleeding events, found similar proportions of events among patients treated with paracetamol (12%), NSAIDs (12.5%) or dipyrone (9%).[74] Some studies indicate that the use of paracetamol can lead to an increase in transaminase levels, but none reported cases of acute liver failure linked to its use; all the dosages involved were the usual ones, up to 4g per day.[76-81]

Dipyrone

The only randomized clinical study that compared the use of paracetamol and dipyrone in the symptomatic treatment of 79 children with dengue and warning signs did not identify significant differences in relation to adverse effects or the progression of the disease.[76] Although two observational studies suggest a possible relationship between the use of dipyrone and progression to more severe forms of dengue[73,82], these studies have notable methodological flaws, such as the absence of adjustments for confounding variables and insufficient sample sizes. Two other observational studies did not show such associations but also suffered from the same methodological problems.[74,83]

Additionally, a systematic review examining the short-term use of dipyrone did not find an increased risk of adverse events compared to paracetamol and NSAIDs. Of the 79 studies analyzed involving 3,716 patients, there were also no reports of agranulocytosis or death. [84]

Benefits

There is a lack of conclusive studies contrasting the efficacy of different drugs in the symptomatic management of dengue patients, leading the choice of treatment to be guided mainly by the safety profile of the drugs. Research into the safety of NSAIDs, dipyrone and paracetamol has limitations and does not provide definitive evidence.

Harms and burden

In the case of NSAIDs, the harms were considered uncertain, and it was also noted that they could be confused with manifestations of severe dengue, such as bleeding. For dipyrone and paracetamol, the panel assessed that the harms are minor, based on the fact that the reported side effects are not life-threatening.

Decision criteria and additional considerations

Although there is no concrete proof that NSAIDs increase the risk of bleeding in these patients, the perception of a more favorable safety profile for paracetamol and dipyrone, added to the fact that both drugs are widely available and well-known by doctors working in emergency services in Brazil, makes the ABRAMEDE panel, together with the recommendations of the Ministry of Health and the WHO, prefer these substances.

Equity in healthcare provision

Paracetamol and dipyrone are widely available in EDs in Brazil, and the panel considered that recommending their use does not compromise equity in patient care.

Conclusions and future research needs

Future research could investigate whether there is a specific regimen of paracetamol and/or dipyrone that is more effective and safer for the symptomatic management of these patients.

Question 9

In adult ED patients with severe dengue and circulatory shock, which vasoactive drug should be indicated as the first choice?

Recommendations

9. In adult ED patients with severe dengue who remain in circulatory shock despite adequate fluid resuscitation, ABRAMEDE suggests the use of noradrenaline as the first-line vasopressor.

Weak recommendation; very low level of evidence

Relevant considerations:

- There was no consensus among the panel members regarding the best time to start the vasopressor in initial care, but it was considered reasonable to start noradrenaline after resuscitation with crystalloids and in parallel with the use of strategies such as colloids in those patients who are refractory.
- The panel considered that the rationale of early initiation of vasoactive drugs may not be beneficial in dengue patients and could lead to fluid under-resuscitation in these patients.
- Adequate fluid resuscitation was considered to be crystalloid replacement with aliquots of 20 ml/kg, repeated up to 3 times or until signs and/or symptoms of congestion appear. In patients with no response to crystalloids and evidence of hemoconcentration, infusion of albumin 0.5 to 1.5 g/kg could also be performed before starting the vasopressor.
- Vasopressor therapy should preferably be guided by targets such as mean arterial pressure, capillary refill time, urine output and lactate.

Summary of evidence

The literature was searched by a medical librarian for the concepts of dengue and vasopressors in the ED, and a total of 23 citations were found with the standardized search. (Appendix 2) All citations were reviewed by two independent methodologists, and none met the predefined eligibility criteria based on the PICO question. Thus, there seems to be no direct evidence in the literature to guide the choice of vasopressors in patients with severe dengue and circulatory shock.

In this context, it is possible to use indirect evidence to decide which vasopressor could be indicated as the first choice. Considering that plasma extravasation secondary to increased capillary permeability is the main pathophysiological mechanism of dengue shock syndrome,[58] after adequate fluid resuscitation with crystalloid solution followed by colloidal solutions, in patients who remain with signs of poor systemic perfusion and show signs of volume overload,[53,85] it is reasonable to start vasoactive drugs with vasoconstrictor properties, such as noradrenaline and vasopressin.[86,87]

Benefits

The available evidence does not support the existence of a benefit in the use of vasoactive drugs (including noradrenaline) in patients with severe dengue and circulatory shock.

It should be noted, however, that the use of vasoactive drugs in patients who continue to show signs of poor perfusion may be necessary. Volume overload has already been shown to have adverse effects, including increased mortality.[88] In addition, specifically in patients with dengue shock syndrome, especially women, malnourished patients, and those who have received prolonged intravenous fluid therapy or bolus administration of volume expansion, have more complications associated with volume overload.[85]

Harms and burden

The initiation of vasopressor does not interrupt the pathophysiological process of plasma extravasation, and re-evaluation for new changes is important in the therapeutic process in patients with dengue shock syndrome.[53]

Complications secondary to the use of vasopressors can be serious and potentially fatal and include severe cardiac arrhythmias, acute myocardial infarction, mesenteric ischemia and limb ischemia.[89]

Decision criteria and additional considerations

Considering that noradrenaline is the first-line vasopressor in patients with undifferentiated shock, especially in patients with distributive shock,[90] and that, in the absence of better evidence, case reports have shown its safe use in patients with dengue shock syndrome,[91,92] this medication is suggested as the first line in patients with an indication to start vasoactive drugs.

Equity in healthcare provision

The limited availability of vasopressin in some EDs reinforces the choice of noradrenaline, as it is more widely available, thus promoting equity in treatment.

Conclusions and future research needs

Future research is essential to determine the benefit of vasopressors, establish the drug and dose of choice, and the ideal timing to start it in patients with severe dengue and circulatory shock.

Question 10

In adult ED patients with severe dengue and hemorrhagic shock who are using antiplatelets and/or anticoagulants, is there a validated specific therapy? If so, which one should be used?

Recommendations

10. In adult ED patients with severe dengue and hemorrhagic shock who are using antiplatelets and/or anticoagulants, there is no evidence to validate specific therapies for reversing these agents. (it was not possible to generate specific recommendations for this question)

Relevant considerations:

- In the presence of life-threatening bleeding (i.e. hemorrhagic shock), both antiaggregants and anticoagulants should be discontinued.
- There was no consensus among the panel members on the application of indirect evidence for the use of reversals in the population of patients with dengue and bleeding. Part of the panel considered it reasonable to use guidelines from other populations (e.g. trauma victims with life-threatening bleeding) to guide treatment[93]. The use of thromboelastometry to guide specific therapies was also discussed as a reasonable option, again using indirect evidence from other populations.

Summary of evidence

The literature was searched by a medical librarian for the concepts of dengue, anticoagulants, antiplatelets and the emergency care context, and a total of 23 citations were found with the standardized search. (Appendix 2) All citations were

reviewed by two independent methodologists and none met the pre-defined eligibility criteria based on the PICO question. Thus, there does not appear to be any direct evidence in the literature to guide specific therapies in patients with severe dengue and hemorrhagic shock who are using antiplatelets or anticoagulants.

There is no randomized clinical trial or more robust evidence evaluating the benefit of platelet transfusion for patients with dengue and significant hemorrhagic manifestations. On the other hand, the risk of immune-mediated platelet lysis has been reported and can destroy donor platelets. However, it seems reasonable to consider platelet transfusion in cases of severe and persistent life-threatening bleeding when thrombocytopenia is present. It should be considered that thrombocytopenia is not the only cause of bleeding, and it is important to assess and correct coagulation abnormalities, particularly if possible with the use of thromboelastography/thromboelastometry, considering the greater inaccuracy of the coagulogram.

There is also no evidence in dengue patients to support the routine use of agents such as recombinant activated factor VII (rFVIIa), IVIg and anti-D globulin, fresh plasma and cryoprecipitate without adequate knowledge of the mechanisms or factors associated with bleeding, extending the use of antidotes or drugs to neutralize anticoagulants in previous use.

Benefits

There is no evidence to guide the reversal of anticoagulants or antiplatelets in patients with dengue and severe hemorrhagic manifestations. If one considers the indirect evidence from other populations with hemorrhagic shock (e.g. trauma), some strategies, such as reversal of warfarin anticoagulation with prothrombin complex, for example, could be considered. In addition, the use of thromboelastometry would also help to define which specific therapies the patient would benefit from based on the more precise identification of coagulation disorders.

Harms and burden

The indiscriminate use of reversal agents in patients with dengue and bleeding could lead to an increase in thrombotic events. This was one of the reasons why there was no consensus among the panel to extrapolate evidence from other populations to apply to patients with dengue and life-threatening bleeding who are taking antiplatelet and/or anticoagulant drugs.

Decision criteria and additional considerations

In not generating specific recommendations for this question, the panel took into account the uncertainty regarding the benefits of reversal agents in the context of severe dengue. Although there is a potential benefit based on biological plausibility, the absence of evidence in the population with dengue and hemorrhagic manifestations was a key criterion.

Equity in healthcare provision

The limited availability of anticoagulant reversals may compromise equity in access to these interventions.

Conclusions and future research needs

In patients with severe dengue and hemorrhagic shock who are using antiplatelets or anticoagulants, there is a need for future studies to evaluate the efficacy and safety of specific reversal agents. In the meantime, extrapolation of hemorrhagic shock management from other populations should be done with caution.

General problems necessary for the correct interpretation and implementation of the recommendations

Limitations

The limitations of this guideline are diverse, including:

- The need to adapt 7 of the 10 questions from a pre-existing guideline, given the urgency of providing guidance to physicians working in

Brazilian EDs. This adaptation reflects the pressure to quickly develop a guideline relevant to the national context, but may limit the specificity and comprehensiveness of the recommendations for the Brazilian reality.

- The restriction to addressing only ten questions due to limited time and resources needed to develop a guideline that would answer a larger number of questions in a methodologically rigorous way. This decision, although intentional to maintain adherence to the GRADE methodology - recognised worldwide and recommended by the WHO for the development of clinical practice guidelines - restricts the scope of the guideline and may leave important gaps in the management of dengue in the emergency setting.
- Most of the recommendations are considered weak and are based on a low level of evidence. This highlights the scarcity of robust evidence available to support stronger recommendations, indicating a critical area where more research is needed.

These limitations highlight the importance of a continuous approach to reviewing and updating the guidelines as new evidence becomes available, as well as the need for investment in research to strengthen the evidence base supporting dengue management in emergency settings.

Preferences and values assumed

In the process of drawing up this guideline, the predominant preferences and values are those of emergency physicians, most of whom work in hospital EDs. However, Emergency Medicine encompasses both care in hospital departments and in emergency care units (UPAs). We also sought to incorporate the perspective of emergency physicians who treat patients in these lower complexity units. In addition, the Brazilian reality of ED overcrowding was considered, highlighting the importance of developing evidence-based guidelines to guide the most efficient use of available resources in the country's EDs.

Implementation considerations

To ensure effective implementation of the recommendations, a careful reading of the relevant considerations associated with each recommendation is crucial, as they clarify nuances related to specific subgroups of patients and consider the applicability of these guidelines within the context of a healthcare system with its particularities. For example, hospitalization criteria were developed by taking into account both public and private health systems. However, it is important to recognise that the final decisions may need to be adapted according to variables not covered by this guideline, reflecting the need for flexibility and careful evaluation on the part of health professionals when applying the recommendations.

PLANNING TO UPDATE THE GUIDELINE

This guideline may be updated in the future if studies emerge and are considered by ABRAMEDE's Clinical Practice Guidelines Committee to be capable of significantly altering the recommended practices and guidelines. With progress in the development of dengue vaccines, it is possible that we will face less intense epidemics in the future and that the production of new evidence on the subject will become even scarcer.

AUTHOR'S CONTRIBUTION

All the authors participated in writing and reviewing this manuscript.

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APPENDIX 1. CONFLICT OF INTEREST

Questions:

1. Are you a qualified emergency physician?
2. Professional relationships: in the last three years, have you had any employment, consultancy, or received fees from any entity that may have an interest in the dengue management guideline? (This includes pharmaceutical companies, medical device manufacturers, professional associations, etc.) If yes, include details.
3. Research and funding: have you or your institution received research funding or other financial support from sources with an interest in the dengue management guideline in the last 3 years? If yes, include details.
4. Publications: in the last three years, have you published or presented any work on dengue or related treatments sponsored by entities with a potential conflict of interest? If yes, include details.

Answers

Certified emergency physician	14/16 (87.5%)
Professional relationships with a potential conflict of interest	2/16 (12.5%)
Research and funding with a potential conflict of interest	0/16 (0.0%)
Publications with a potential conflict of interest	0/16 (0.0%)

The two members who reported potential conflicts of interest concerning professional relationships are AstraZeneca speakers.

APPENDIX 2. DETAILED LITERATURE SEARCHES

Dengue and point-of-care ultrasound

Databases & Registers	# of initial hits
Central	2
CINAHL	7
ClinicalTrials.gov	2
Embase	46
ICTRP	0
Medline	12
SciELO	0
Scopus	4
Web of Science	8
Totals	81

Duplicates Removed by Covidence - 26

Search strategies for the article appendix:

ClinicalTrials.gov (2000+):

dengue AND emergency AND (ultrasound OR ultrasonography OR sonography OR sonogram OR sonographic OR echography OR POCUS)

CINAHL with Full Text via EBSCO (1963+):

S4	S1 AND S2 AND S3
S3	(MH "Ultrasonography") OR (ultraso* or sonogra* or echo* or POCUS)
S2	(MH "Emergency Service+" OR MH "Emergency Patients" OR MH "Emergency Room Visits" OR MH "Emergency Medicine") OR TI(((emergency or A-and-E or A-E or A&E or A-&-E) N2 (department* or medicine or room* or unit* or ward*)) or urgent-care or emergicent*) OR AB(((emergency or A-and-E or A-E or A&E or A-&-E) N2 (department* or medicine or room* or unit* or ward*)) or urgent-care or emergicent*) OR SO(Emergency)
S1	(MH "Dengue+") OR TI(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkock or Thai or Philippine* or Filipin* or Singapore*) N1 fever)) OR AB(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) N1 fever))

Cochrane Central Register of Controlled Trials (CCTR) via Ovid (1991+)):

#	Query	Results from 21 Feb 2024
1	(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) adj1 fever)).ab,hw,ti.	894
2	(((emergency or A-and-E or A-E or AE or A&E or A-&-E) adj2 (department* or medicine or room* or unit* or ward*)) or urgent-care or emergicent*).ab,hw,ti,jw. or (ED or ER).ti.	23,023
3	(ultraso* or sonogra* or echo* or POCUS).ab,hw,ti.	79,720
4	1 and 2 and 3	2

Embase via Ovid (1974+):

#	Query	Results from 21 Feb 2024
1	exp Dengue virus/ or exp dengue/	37,464
2	(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) adj1 fever)).ab,kf,ti,dq.	36,799
3	or/1-2	43,037
4	emergency ward/ or hospital emergency service/ or emergency physician/ or emergency medicine/ or (((emergency or A-and-E or A-E or AE or A&E or A-&-E) adj2 (department* or medicine or room* or unit* or ward*)) or urgent-care or emergicent*).ab,kf,ti,dq,ox,hw,jx. or (ED or ER).ti.	426,309
5	"point of care ultrasound"/ or exp echography/ or (ultraso* or sonogra* or echo* or POCUS).ab,kf,ti,dq.	1,525,573
6	3 and 4 and 5	66
7	limit 6 to (english or portuguese or spanish)	66
8	limit 7 to conference abstract	20
9	7 not 8	46

International Clinical Trials Registry Platform (**ICTRP**) from the World Health Organization (2005+) – *standard interface*:
dengue AND emergency AND (ultraso* OR sonogra* OR echo* OR POCUS)

MEDLINE via Ovid (1946+ and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily):

#	Query	Results from 21 Feb 2024
1	exp Dengue/ or Dengue Virus/	19,874
2	(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) adj1 fever)).ab,kf,ti.	29,217
3	or/1-2	30,256
4	Emergency Service, Hospital/ or Emergency Medicine/ or (((emergency or A-and-E or A-E or AE or A&E or A-&-E) adj2 (department* or medicine or room* or unit* or ward*)) or urgent-care or emergicent*).ab,kf,ti,hw,jw. or (ED or ER).ti.	264,183
5	Ultrasonography/ or (ultraso* or sonogra* or echo* or POCUS).ab,kf,ti.	799,366
6	3 and 4 and 5	12

SciELO

#4	#1 AND #2 AND #3
#3	TS=(ultraso* or ecograf* or POCUS)
#2	TS=(emergenc*) OR SO=(emergenc*)
#1	TS=(Dengue or DENV)

Scopus via Elsevier (1788+):
((TITLE-ABS-KEY (dengue OR denv) OR TITLE-ABS-KEY ((aden OR bouquet OR break-bone OR breakbone OR dandy OR solar OR sun OR bangkok OR thai OR philippine* OR filipin* OR singapore*) W/1 fever))) AND ((TITLE-ABS-KEY ((emergency OR a-and-e OR a-e OR a&e OR a-&-e) W/2 (department* OR medicine OR room* OR unit* OR ward*)) OR TITLE-ABS-KEY (urgent-care OR emergicent*) OR TITLE (ed OR er) AND SRCTITLE (emergency))) AND (TITLE-ABS-KEY (ultraso* OR sonogra* OR echo* OR pocus))

Web of Science Core Collection via Clarivate Analytics (Science Citation Index Expanded 1975+ & Emerging Sources Citation Index 2015+):

#4	#1 AND #2 AND #3
#3	TS=(ultraso* or sonogra* or echo* or POCUS)
#2	TS=((emergency or A-and-E or A-E or A&E or A-&-E) NEAR/2 (department* or medicine or room* or unit* or ward*)) OR TS=(urgent-care or emergicent*) OR TI=(ED or ER) OR SO=(emergency)
#1	Dengue or DENV (Topic) or (Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) NEAR/1 fever (Topic)

Dengue e uso de vasopressores

Databases & Registers	# of initial hits
Central	0
ClinicalTrials.gov	0
Embase	17
ICTRP	0
Medline	1
SciELO	1
Scopus	3
Web of Science	1
Totals	23

Duplicates Removed by Covidence - 5
Search strategies for the article appendix:
ClinicalTrials.gov (2000+):
dengue AND emergency AND (vasoactive OR vasoconstrictor OR vasopressor OR pressor OR vasopressin OR vasopressins OR Phenylephrine OR Epinephrine OR Norepinephrine OR Dopamine OR angiotensin OR Terlipressin)

Cochrane Central Register of Controlled Trials (CCTR) via Ovid (1991+)):

#	Query	Results from 21 Feb 2024
1	(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) adj1 fever)).ab,hw,ti.	894
2	Emergency Service, Hospital/ or Emergency Medicine/ or (((emergency or A-and-E or A-E or AE or A&E or A-&-E) adj2 (department* or medicine or room* or unit* or ward*)) or urgent-care or emergicent*).ab,hw,ti,jw. or (ED or ER).ti.	23,327
3	(vasoactive or vasoconstrict* or vasopressor* or pressor*).ab,hw,ti.	13,615
4	(vasopressin* or antidiuretic-hormone* or anti-diuretic-hormone* or ADH or AVP or beta-hypophamine or diapid or lypressin or ornipressin or orpressin or pitressin or postacton or pressyn or vasophysin or vasopin or vasostrict or vassopressin* or argipressin or copeptin or desmopressin* or adin or adiuretin or concentraid or dav-ritter or DDAVP or deaminovasopressin or defirin or desmirin or desmogalen or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin* or minrin or minurin or miram or nictur or niwinas or nocdurna or noctisson or noctiva or nocturin or nocutil or nokdirna or noqdirna or noqturina or nordurine or novidin or nucotil or octim or octostim or presinex or pseurin or stimate or wetirin or felypressin or felipressin or fellypressin or octapressin* or octopressin or lypressin* or dialip or diapid or lysinevasopressin or lysopressin or postacton or syntopressin or orgipressin or pressinoic-acid or selepressin or terlipressin* or glipressin* or glycylpressin* or glypressin* or lucassin or remestyp or stemflova or terlipresin* or terlivaz or triglycyllypressin or triglycyllysylvasopressin or triglycylvasopressin or variquel).ab,hw,ti.	4,540
5	(Phenylephrine or Etilefrin* or metaoxedrin or metasympatol or mezaton or neosynephrin* or adrianol or albalon or alconefrin or almefrin or anosin or biomidrin or biomydrin or biorphen or davinefrina or derizene or despec or disneumon or dristan or drosin or efrin or efrisel or fenefrin or fenylephrine or idrianol or immphentiv or isonefrine or isophrin* or isoptofrin or synephrine or phenylefrine or lexatol or mesaton* or meta-sympathol or metaoxedrin* or metasynephrine or mirazul or mydfrin or sinefrina or neofrin or neooxedrine or neophryn or neosynephrin or neosynesin* or optistin or phenoptic or phenylefrine or phenylephedrine or prefrin or rectasol or rhinall or sucraphen or vazculep or visadron or vistafrin or vistosan or adrenam or adrianol or bioflutin or cardanat or circupon or effortil or efortil or ethyladrianol or ethylnorphenylephrine or ethylphenylephrine or fetanol or phetanol or thomasin).ab,hw,ti.	2,621
6	(epinephrin* or racepinephrine or adrenalin* or epifrin or epitrate or lyophrin or micronefrin or micronephrine or vaponefrin or adnephrin* or adrenal-hydrochloride or adrenamine or adrenapax or adrenazin or adrenine or adrin* or advaradin or asthmahaler or balmadren or biorenine or bosmin or bronitin or bronkaid or chelafrin or drenamist or dylephrin or dyspne-inhal or epiglaufrin or epimephrine or epinephran or epirenamine or epirenan or exadrin or glaucon or glaucosan or glaufrin or glin-epin or glycirenan or haemostatin or hemisine or hemostasin or hemostatin or hypernephrin or isopto-epinal or levoadrenalin* or levoepinephrine or levorenin or levorenine or methylaminoethanolcatechol or methylarterenol or mucidrina or myosthenine or methylnoradrenalin or neffy or nephridine or nieraline or paranephrin or posumin or primatene or renaglandin or renaglandulin or renaleptine or renalin* or renoform or renostypticin or renostyptin or scurenaline or simplene or soladren or sphygmogenin or styptirenal or supracapsulin or supranephrane or supranephrin or supranol or suprarenaline or suprarenin or suprarenine or suprel or surenine or surrenine or susphrine or symjepi or sympathin or takamina or tonogen or trenamist or vasoconstrictine or vasodrine or vasotonin or weradren).ab,hw,ti.	11,988
7	(norepinephrin* or arterenol or levarterenol or levonor or levonorepinephrine or levophed or noradrenalin* or adrenor or alginodia or arterenal or arterenol or baycain-green or neomelubrin or noradrec or noradrine or norexadrin or revarterenol or sympathin).ab,hw,ti.	9,496
8	(dopamin* or hydroxytyramine or intropin or cardiopal or cardiosteril or catabon or dihydroxyphenylethylamine or docard or dopamex or dopaminex or dopaminum or dopastat or dopinga or dopmin or drynalken or dynatra or dynosgiludop or inopan or inopin or inotropin or inovan or levodopamine or revivan or tensamin or uramin).ab,hw,ti.	10,465
9	((angiotensin adj1 ("2" or II or amide)) or delivert or giapreza or hypertensin or saralasin or sarile).ab,hw,ti.	5,700

#	Query	Results from 21 Feb 2024
10	(terlipresin* or terlipressin* or terlypressin* or glipressin* or glycylpressin* or glypressin* or lucassin or remestyp or stemflova or tglvp or terlivaz or triglycyllypressin or triglycyllysylvasopressin or triglycylvasopressin or variquel).ab,hw,ti.	592
11	or/3-10	47,801
12	1 and 2 and 11	0

Embase via Ovid (1974+):

#	Query	Results from 21 Feb 2024
1	exp Dengue virus/ or exp dengue/	37,468
2	(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) adj1 fever)).ab,kf,ti,dq.	36,803
3	or/1-2	43,041
4	emergency ward/ or hospital emergency service/ or emergency physician/ or emergency medicine/ or (((emergency or A-and-E or A-E or AE or A&E or A-&-E) adj2 (department* or medicine or room* or unit* or ward*)) or urgent-care or emergicent*).ab,kf,ti,dq,ox,hw,jx. or (ED or ER).ti.	426,358
5	hypertensive factor/ or vasoconstrictor agent/ or vasoactive agent/ or (vasoactive or vasoconstrict* or vasopressor* or pressor*).ab,kf,ti,dq,dy,tn.	162,453
6	vasopressin/ or exp vasopressin derivative/ or (vasopressin* or antidiuretic-hormone* or anti-diuretic-hormone* or ADH or AVP or beta-hypophamine or diapid or lypressin or ornipressin or orpressin or pitressin or postacton or pressyn or vasophysin or vasopin or vasostrict or vassopressin* or argipressin or copeptin or desmopressin* or adin or adiuretin or concentraid or dav-ritter or DDAVP or deaminovasopressin or defirin or desmirin or desmogalen or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin* or minrin or minurin or miram or nictur or niwinas or nocdurna or noctisson or noctiva or nocturin or nocutil or nokdirna or noqdirna or noqturina or nordurine or novidin or nucotil or octim or octostim or presinex or pseurin or stimate or wetirin or felypressin or felipressin or fellypressin or octapressin* or octopressin or lypressin* or dialip or diapid or lysinevasopressin or lysopressin or postacton or syntopressin or orgipressin or pressinoic-acid or selepressin or terlipressin* or glipressin* or glycylpressin* or glypressin* or lucassin or remestyp or stemflova or terlipresin* or terlivaz or triglycyllypressin or triglycyllysylvasopressin or triglycylvasopressin or variquel).ab,kf,ti,dq,dy,tn.	94,653
7	phenylephrine/ or (Phenylephrine or Etilefrin* or metaoxedrin or metasympatol or mezaton or neosynephrin* or adrianol or albalon or alconefrin or almefrin or anosin or biomidrin or biomydrin or biorphen or davinefrina or derizene or despec or disneumon or dristan or drosin or efrin or efrisel or fenefrin or fenylephrine or idrianol or immphentiv or isonefrine or isophrin* or isoptofrin or synephrine or phenylefrine or lexatol or mesaton* or meta-sympathol or metaoxedrin* or metasynephrine or mirazul or mydfrin or sinefrina or neofrin or neooxedrine or neophryn or neosynephrin or neosynesin* or optistin or phenoptic or phenylefrine or phenylephedrine or prefrin or rectasol or rhinall or sucraphen or vazculep or visadron or vistafrin or vistosan or adrenam or adrianol or bioflutin or cardanat or circupon or effortil or efortil or ethyladrianol or ethylnorphenylephrine or ethylphenylephrine or fetanol or phetanol or thomasin).ab,kf,ti,dq,dy,tn.	44,889
8	exp epinephrine/ or (epinephrin* or racepinephrine or adrenalin* or epifrin or epitrate or lyophrin or micronefrin or micronephrine or vaponefrin or adnephrin* or adrenal-hydrochloride or adrenamine or adrenapax or adrenazin or adrenine or adrin* or advaradin or asthmahaler or balmadren or biorenine or bosmin or bronitin or bronkaid or chelafrin or drenamist or dylephrin or dyspne-inhal or epiglaufrin or epimephrine or epinephran or epirenamine or epirenan or exadrin or glaucon or glaucosan or glaufrin or glin-epin or glycirenan or haemostatin or hemisine or hemostasin or hemostatin or hypernephrin or isopto-epinal or levoadrenalin* or levoepinephrine or levorenin or levorenine or methylaminoethanolcatechol or methylarterenol or mucidrina or myosthenine or methylnoradrenalin or neffy or nephridine or nieraline or paranephrin or posumin or primatene or renaglandin or renaglandulin or renaleptine or renalin* or renoform or renostypticin or renostyptin or scurenaline or simplene or soladren or sphygmogenin or styptirenal or supracapsulin or supranephrane or supranephrin or supranol or suprarenaline or suprarenin or suprarenine or suprel or surenine or surrenine or susphrine or symjepi or sympathin or takamina or tonogen or trenamist or vasoconstrictine or vasodrine or vasotonin or weradren).ab,kf,ti,dq,dy,tn.	136,262
9	exp noradrenalin/ or (norepinephrin* or arterenol or levarterenol or levonor or levonorepinephrine or levophed or noradrenalin* or adrenor or alginodia or arterenal or arterenol or baycain-green or neomelubrin or noradrec or noradrine or norexadrin or revarterenol or sympathin).ab,kf,ti,dq,dy,tn.	182,785

#	Query	Results from 21 Feb 2024
10	dopamine/ or (dopamin* or hydroxytyramine or intropin or cardiopal or cardiosteril or catabon or dihydroxyphenylethylamine or docard or dopamex or dopaminex or dopaminum or dopastat or dopinga or dopmin or drynalken or dynatra or dynosgiludop or inopan or inopin or inotropin or inovan or levodopamine or revivan or tensamin or uramin).ab,kf,ti,dq,dy,tn.	285,698
11	angiotensin II/ or ((angiotensin adj1 ("2" or II or amide)) or delivert or giapreza or hypertensin or saralasin or sarile).ab,kf,ti,dq,dy,tn.	92,684
12	terlipressin/ or (terlipresin* or terlipressin* or terlypressin* or glipressin* or glycylpressin* or glypressin* or lucassin or remestyp or stemflova or tglvp or terlivaz or triglycyllypressin or triglycyllysylvasopressin or triglycylvasopressin or variquel).ab,kf,ti,dq,dy,tn.	3,890
13	or/5-12	820,782
14	3 and 4 and 13	22
15	limit 14 to (english or portuguese or spanish)	21
16	limit 15 to conference abstract	4
17	15 not 16	17

International Clinical Trials Registry Platform (**ICTRP**) from the World Health Organization (2005+) – *standard interface*:
dengue AND emergency AND (vasoactive OR vasoconstrictor OR vasopressor OR pressor OR vasopressin* OR Phenylephrine OR Epinephrine OR Norepinephrine OR Dopamine OR angiotensin OR Terlipressin)

MEDLINE via Ovid (1946+ and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily):

#	Query	Results from 21 Feb 2024
1	exp Dengue/ or Dengue Virus/	19,875
2	(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) adj1 fever)).ab,kf,ti.	29,214
3	or/1-2	30,253
4	Emergency Service, Hospital/ or Emergency Medicine/ or (((emergency or A-and-E or A-E or AE or A&E or A-&-E) adj2 (department* or medicine or room* or unit* or ward*)) or urgent-care or emergicent*).ab,kf,ti,hw,jw. or (ED or ER).ti.	264,203
5	Vasoconstrictor Agents/ or (vasoactive or vasoconstrict* or vasopressor* or pressor*).ab,kf,ti,nm.	116,869
6	exp Vasopressins/ or (vasopressin* or antidiuretic-hormone* or anti-diuretic-hormone* or ADH or AVP or beta-hypophamine or diapid or lypressin or ornipressin or orpressin or pitressin or postacton or pressyn or vasophysin or vasopin or vasostrict or vassopressin* or argipressin or copeptin or desmopressin* or adin or adiuretin or concentraid or dav-ritter or DDAVP or deaminovasopressin or defirin or desmirin or desmogalen or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin* or minrin or minurin or miram or nictur or niwinas or nocdurna or noctisson or noctiva or nocturin or nocutil or nokdirna or noqdirna or noqturina or nordurine or novidin or nucotil or octim or octostim or presinex or pseurin or stimate or wetirin or felypressin or felipressin or fellypressin or octapressin* or octopressin or lypressin* or dialip or diapid or lysinevasopressin or lysopressin or postacton or syntopressin or orgipressin or pressinoic-acid or selepressin or terlipressin* or glipressin* or glycylpressin* or glypressin* or lucassin or remestyp or stemflova or terlipresin* or terlivaz or triglycyllypressin or triglycyllysylvasopressin or triglycylvasopressin or variquel).ab,kf,ti,nm.	63,180

#	Query	Results from 21 Feb 2024
7	exp Phenylephrine/ or (Phenylephrine or Etilefrin* or metaoxedrin or metasympatol or mezaton or neosynephrin* or adrianol or albalon or alconefrin or almefrin or anosin or biomidrin or biomydrin or biorphen or davinefrina or derizene or despec or disneumon or dristan or drosin or efrin or efrisel or fenefrin or fenylephrine or idrianol or immphentiv or isonefrine or isophrin* or isoptofrin or synephrine or phenylefrine or lexatol or mesaton* or meta-sympathol or metaoxedrin* or metasynephrine or mirazul or mydfrin or sinefrina or neofrin or neooxedrine or neophryn or neosynephrin or neosynesin* or optistin or phenoptic or phenylefrine or phenylephedrine or prefrin or rectasol or rhinall or sucraphen or vazculep or visadron or vistafrin or vistosan or adrenam or adrianol or bioflutin or cardanat or circupon or effortil or efortil or ethyladrianol or ethylnorphenylephrine or ethylphenylephrine or fetanol or phetanol or thomasin).ab,kf,ti,nm.	24,524
8	exp Epinephrine/ or (epinephrin* or racepinephrine or adrenalin* or epifrin or epitrate or lyophrin or micronefrin or micronephrine or vaponefrin or adnephrin* or adrenal-hydrochloride or adrenamine or adrenapax or adrenazin or adrenine or adrin* or advaradin or asthmahaler or balmadren or biorenine or bosmin or bronitin or bronkaid or chelafrin or drenamist or dylephrin or dyspne-inhal or epiglaufrin or epimephrine or epinephran or epirenamine or epirenan or exadrin or glaucon or glaucosan or glaufrin or glin-epin or glycirenan or haemostatin or hemisine or hemostasin or hemostatin or hypernephrin or isopto-epinal or levoadrenalin* or levoepinephrine or levorenin or levorenine or methylaminoethanolcatechol or methylarterenol or mucidrina or myosthenine or methylnoradrenalin or neffy or nephridine or nieraline or paranephrin or posumin or primatene or renaglandin or renaglandulin or renaleptine or renalin* or renoform or renostypticin or renostyptin or scurenaline or simplene or soladren or sphygmogenin or styptirenal or supracapsulin or supranephrane or supranephrin or supranol or suprarenaline or suprarenin or suprarenine or suprel or surenine or surrenine or susphrine or symjepi or sympathin or takamina or tonogen or trenamist or vasoconstrictine or vasodrine or vasotonin or weradren).ab,kf,ti,nm.	83,751
9	exp Norepinephrine/ or (norepinephrin* or arterenol or levarterenol or levonor or levonorepinephrine or levophed or noradrenalin* or adrenor or alginodia or arterenal or arterenol or baycain-green or neomelubrin or noradrec or noradrine or norexadrin or revarterenol or sympathin).ab,kf,ti,nm.	131,132
10	exp Dopamine/ or (dopamin* or hydroxytyramine or intropin or cardiopal or cardiosteril or catabon or dihydroxyphenylethylamine or docard or dopamex or dopaminex or dopaminum or dopastat or dopinga or dopmin or drynalken or dynatra or dynosgiludop or inopan or inopin or inotropin or inovan or levodopamine or revivan or tensamin or uramin).ab,kf,ti,nm.	204,171
11	exp Angiotensin II/ or ((angiotensin adj1 (“2” or II or amide)) or delivert or giapreza or hypertensin or saralasin or sarile).ab,kf,ti,nm.	71,810
12	Terlipressin/ or (terlipresin* or terlipressin* or terlypressin* or glipressin* or glycylpressin* or glypressin* or lucassin or remestyp or stemflova or tglvp or terlivaz or triglycyllypressin or triglycyllysylvasopressin or triglycylvasopressin or variquel).ab,kf,ti,nm.	1,244
13	or/5-12	571,286
14	3 and 4 and 13	1
15	limit 14 to (english or portuguese or spanish)	1

SciELO via Clarivate (2002+)

#6	#1 AND #2 AND #5
#5	#3 OR #4
#4	TS=(vasopressin* or phenylephrine or epinephrin* or norepinephrin* or dopamin* or angiotensin or terlipressin or Pitressin or Vasostrict or Biorphen® or Vazculep)
#3	TS=(vasoactive or vasoconstrict* or vasoativo or vasoactivo or vasoconstritor* or vasopressor* or vasopresor* or pressor* or presor*)
#2	TS=(emergenc*) OR SO=(emergenc*)
#1	TS=(Dengue)

Scopus via Elsevier (1788+):

(((TITLE-ABS-KEY (dengue OR denv) OR TITLE-ABS-KEY ((aden OR bouquet OR break-bone OR breakbone OR dandy OR solar OR sun OR bangok OR thai OR philippine* OR filipin* OR singapore*) W/1 fever))) AND ((TITLE-ABS-KEY ((emergency OR a-and-e OR a-e OR a&e OR a-&-e) W/2 (department* OR medicine OR room* OR unit* OR ward*)) OR TITLE-ABS-KEY (urgent-care OR emergicent*) OR TITLE (ed OR er) AND SRCTITLE (emergency)))) AND ((TITLE-ABS-KEY (vasoactive OR vasoconstrict* OR vasopressor* OR pressor*)) OR (TITLE-ABS-KEY (vasopressin* OR antidiuretic-hormone* OR anti-diuretic-hormone* OR adh OR avp OR beta-hypophamine OR diapid OR lypressin OR ornipressin OR orpressin OR pitressin OR postacton OR pressyn OR vasophysin OR vasopin OR vasostrict OR vassopressin* OR argipressin OR copeptin OR desmopressin* OR adin OR adiuretin OR concentraid OR dav-ritter OR ddavp OR deaminovasopressin OR defirin OR desmirin OR desmogalen OR desmomelt OR desmopresina OR desmospray OR desmotab* OR desurin OR emosint OR enupresol OR minirin* OR minrin OR minurin OR miram OR nictur OR niwinas OR nocdurna OR noctisson OR noctiva OR nocturin OR nocutil OR nokdirna OR noqdirna OR noqturina OR nordurine OR novidin OR nucotil OR octim OR octostim OR presinex OR pseurin OR stimate OR wetirin OR felypressin OR felipressin OR fellypressin OR octapressin* OR octopressin OR lypressin* OR dialip OR diapid OR lysinevasopressin OR lysopressin OR postacton OR syntopressin OR orgipressin OR pressinoic-acid OR selepressin OR terlipressin* OR glipressin* OR glycylpressin* OR glypressin* OR lucassin OR remestyp OR stemflova OR terlipresin* OR terlivaz OR triglycyllypressin OR triglycyllysylvasopressin OR triglycylvasopressin OR variquel)) OR (TITLE-ABS-KEY (phenylephrine OR etilefrin* OR metaoxedrin OR metasympatol OR mezaton OR neosynephrin* OR adrianol OR albalon OR alconefrin OR almefrin OR anosin OR biomidrin OR biomydrin OR biorphen OR davinefrina OR derizene OR despec OR disneumon OR dristan OR drosin OR efrin OR efrisel OR fenefrin OR fenylephrine OR idrianol OR immphentiv OR isonefrine OR isophrin* OR isoptofrin OR synephrine OR phenylefrine OR lexatol OR mesaton* OR meta-sympathol OR metaoxedrin* OR metasynephrine OR mirazul OR mydfrin OR sinefrina OR neofrin OR neooxedrine OR neophryn OR neosynephrin OR neosynesin* OR optistin OR phenoptic OR phenylefrine OR phenylephedrine OR prefrin OR rectasol OR rhinall OR sucraphen OR vazculep OR visadron OR vistafrin OR vistosan OR adrenam OR adrianol OR bioflutin OR cardanat OR circupon OR effortil OR efortil OR ethyladrianol OR ethylnorphenylephrine OR ethylphenylephrine OR fetanol OR phetanol OR thomasin)) OR (TITLE-ABS-KEY (epinephrin* OR racepinephrine OR adrenalin* OR epifrin OR epitrate OR lyophrin OR micronefrin OR micronephrine OR vaponefrin OR adnephrin* OR adrenal-hydrochloride OR adrenamine OR adrenapax OR adrenazin OR adrenine OR adrin* OR advaradin OR asthmahaler OR balmadren OR biorenine OR bosmin OR bronitin OR bronkaid OR chelafrin OR drenamist OR dylephrin OR dyspne-inhal OR epiglaufrin OR epimephrine OR epinephran OR epirenamine OR epirenan OR exadrin OR glaucon OR glaucosan OR glaufrin OR glin-epin OR glycirenan OR haemostatin OR hemisine OR hemostasin OR hemostatin OR hypernephrin OR isopto-epinal OR levoadrenalin* OR levoepinephrine OR levorenin OR levorenine OR methylaminoethanolcatechol OR methylarterenol OR mucidrina OR myosthenine OR methylnoradrenalin OR neffy OR nephridine OR nieraline OR paranephrin OR posumin OR primatene OR renaglandin OR renaglandulin OR renaleptine OR renalin* OR renoform OR renostypticin OR renostyptin OR scurenaline OR simplene OR soladren OR sphygmogenin OR styptirenal OR supracapsulin OR supranephrane OR supranephrin OR supranol OR suprarenaline OR suprarenin OR suprarenine OR suprel OR surenine OR surrenine OR susphrine OR symjepi OR sympathin OR takamina OR tonogen OR trenamist OR vasoconstrictine OR vasodrine OR vasotonin OR weradren)) OR (TITLE-ABS-KEY (norepinephrin* OR arterenol OR levarterenol OR levonor OR levonorepinephrine OR levophed OR noradrenalin* OR adrenor OR alginodia OR arterenal OR arterenol OR baycain-green OR neomelubrin OR noradrec OR noradrine OR norexadrin OR revarterenol OR sympathin)) OR (TITLE-ABS-KEY (dopamin* OR hydroxytyramine OR intropin OR cardiopal OR cardiosteril OR catabon OR dihydroxyphenylethylamine OR docard OR dopamex OR dopaminex OR dopaminum OR dopastat OR dopinga OR dopmin OR drynalken OR dynatra OR dynosgiludop OR inopan OR inopin OR inotropin OR inovan OR levodopamine OR revivan OR tensamin OR uramin)) OR (TITLE-ABS-KEY ((angiotensin W/1 ("2" OR ii OR amide)) OR delivert OR giapreza OR hypertensin

OR saralasin OR sarile)) OR (TITLE-ABS-KEY (terlipresin* OR terlipressin* OR terlypressin* OR glipressin* OR glycylpressin* OR glypressin* OR lucassin OR remestyp OR stemflova OR tglvp OR terlivaz OR triglycyllypressin OR triglycyllysylvasopressin OR triglycylvasopressin OR variquel)))

Web of Science Core Collection via Clarivate Analytics (Science Citation Index Expanded 1975+ & Emerging Sources Citation Index 2015+):

#12	#1 AND #2 AND #11
#11	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#10	TS=(terlipresin* or terlipressin* or terlypressin* or glipressin* or glycylpressin* or glypressin* or lucassin or remestyp or stemflova or tglvp or terlivaz or triglycyllypressin or triglycyllysylvasopressin or triglycylvasopressin or variquel)
#9	TS=((angiotensin NEAR/1 ("2" or II or amide)) or delivert or giapreza or hypertensin or saralasin or sarile)
#8	TS=(dopamin* or hydroxytyramine or intropin or cardiopal or cardiosteril or catabon or dihydroxyphenylethylamine or docard or dopamex or dopaminex or dopaminum or dopastat or dopinga or dopmin or drynalken or dynatra or dynosgiludop or inopan or inopin or inotropin or inovan or levodopamine or revivan or tensamin or uramin)
#7	TS=(norepinephrin* or arterenol or levarterenol or levonor or levonorepinephrine or levophed or noradrenalin* or adrenor or alginodia or arterenal or arterenol or baycain-green or neomelubrin or noradrec or noradrine or norexadrin or revarterenol or sympathin)
#6	TS=(epinephrin* or racepinephrine or adrenalin* or epifrin or epitrate or lyophrin or micronefrin or micronephrine or vaponefrin or adnephrin* or adrenal-hydrochloride or adrenamine or adrenapax or adrenazin or adrenine or adrin* or advaradin or asthmahaler or balmadren or biorenine or bosmin or bronitin or bronkaid or chelafrin or drenamist or dylephrin or dyspne-inhal or epiglaufrin or epimephrine or epinephran or epirenamine or epirenan or exadrin or glaucon or glaucosan or glaufrin or glin-epin or glycirenan or haemostatin or hemisine or hemostasin or hemostatin or hypernephrin or isopto-epinal or levoadrenalin* or levoepinephrine or levorenin or levorenine or methylaminoethanolcatechol or methylarterenol or mucidrina or myosthenine or methylnoradrenalin or neffy or nephridine or nieraline or paranephrin or posumin or primatene or renaglandin or renaglandulin or renaleptine or renalin* or renoform or renostypticin or renostyptin or scurenaline or simplene or soladren or sphygmogenin or styptirenal or supracapsulin or supranephrane or supranephrin or supranol or suprarenaline or suprarenin or suprarenine or suprel or surenine or surrenine or susphrine or symjepi or sympathin or takamina or tonogen or trenamist or vasoconstrictine or vasodrine or vasotonin or weradren)
#5	TS=(Phenylephrine or Etilefrin* or metaoxedrin or metasympatol or mezaton or neosynephrin* or adrianol or albalon or alconefrin or almefrin or anosin or biomidrin or biomydrin or biorphen or davinefrina or derizene or despec or disneumon or dristan or drosin or efrin or efrisel or fenefrin or fenylephrine or idrianol or immphentiv or isonefrine or isophrin* or isoptofrin or synephrine or phenylefrine or lexatol or mesaton* or meta-sympathol or metaoxedrin* or metasynephrine or mirazul or mydfrin or sinefrina or neofrin or neooxedrine or neophryn or neosynephrin or neosynesin* or optistin or phenoptic or phenylefrine or phenylephedrine or prefrin or rectasol or rhinall or sucraphen or vazculep or visadron or vistafrin or vistosan or adrenam or adrianol or bioflutin or cardanat or circupon or effortil or efortil or ethyladrianol or ethylnorphenylephrine or ethylphenylephrine or fetanol or phetanol or thomasin)
#4	TS=(vasopressin* or antidiuretic-hormone* or anti-diuretic-hormone* or ADH or AVP or beta-hypophamine or diapid or lypressin or ornipressin or orpressin or pitressin or postacton or pressyn or vasophysin or vasopin or vasostrict or vassopressin* or argipressin or copeptin or desmopressin* or adin or adiuretin or concentraid or dav-ritter or DDAVP or deaminovasopressin or defirin or desmirin or desmogalen or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin* or minrin or minurin or miram or nictur or niwinas or nocdurna or noctisson or noctiva or nocturin or nocutil or nokdirna or noqdirna or noqturina or nordurine or novidin or nucotil or octim or octostim or presinex or pseurin or stimate or wetirin or felypressin or felipressin or fellypressin or octapressin* or octopressin or lypressin* or dialip or diapid or lysinevasopressin or lysopressin or postacton or syntopressin or orgipressin or pressinoic-acid or selepressin or terlipressin* or glipressin* or glycylpressin* or glypressin* or lucassin or remestyp or stemflova or terlipresin* or terlivaz or triglycyllypressin or triglycyllysylvasopressin or triglycylvasopressin or variquel)
#3	TS=(vasoactive or vasoconstrict* or vasopressor* or pressor*)
#2	TS=((emergency or A-and-E or A-E or A&E or A-&-E) NEAR/2 (department* or medicine or room* or unit* or ward*)) OR TS=(urgent-care or emergicent*) OR TI=(ED or ER) OR SO=(emergency)
#1	Dengue or DENV (Topic) or (Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) NEAR/1 fever (Topic) (Topic)

Dengue and the use of antiaggregants, anticoagulants and reversal agents

Databases & Registers	# of initial hits
Central	16
ClinicalTrials.gov	4
Embase	15
ICTRP	0
Medline	3
SciELO	0
Scopus	1
Web of Science	4
Totals	43

Duplicates Removed by Covidence - 8
Clinical Trials Registry Results (if using a more detailed PRISMA diagram) – 20
Search strategies for the article appendix:
ClinicalTrials.gov (2000+):
dengue AND (anticoagulant OR antithrombotic OR antithrombin OR antithrombocytic OR "clotting inhibitor" OR "platelet inhibitor" OR antiplatelet OR (thrombocyte AND inhibitor) OR heparin OR hirudin OR coumadin OR warfarin OR aspirin)

Cochrane Central Register of Controlled Trials (CCTR) via Ovid (1991+)):

#	Query	Results from 22 Feb 2024
1	(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) adj1 fever)).ab,hw,ti.	894
2	(anticoagula* or anti-coagula* or antithromb* or anti-thromb* or thrombin-inhibit* or ((platelet* or thromb* or coagulat* or clot* or factor or glycoprotein) adj1 (inhibit* or antagonist* or block*)) or antiaggregant* or anti-aggregant* or antiplatelet* or anti-platelet* or DAPT).ab,hw,ti.	29,787
3	(anisindione or anpocogin or antivitamin-K or anti-vitamin-K or apolate-sodium or beciparcil or chlorophacinone or citrate-trisodium or coumarin or defibrotide or dextran-sulfate or diphenadione or fluindione or ghilanten or glycerophosphoinositol-inositolphosphodiesterase or glycosaminoglycan-polysulfate or heparin* or iliparcil or inclacumab or mopidamol or naroparcil or phenindione or tecarfarin or torapsel or tretoquinol or uproleselan or acetylsalicylic-acid or pseudoephedrine or ajoene or aloxiprin or alprostadil-alfadex or anagrelide or ancrod or applaggin or aprosulate or aspirin or ataprost or atopaxar or beraprost or buflomedil-pyridoxal-phosphate or cangrelor or caplacizumab or cicaprost or cilostazol or ciprostene or clopidogrel or cryptolepine or dazoxiben or dehydrocilostazol or dermatan or dextran or dipyridamole or elinogrel or enfenamic-acid or esuberaprost or glenzocimab or heparan-sulfate or ifetroban or iloprost or imolamine or indobufen or isbogrel or itazigrel or linotroban or lixazinone or mipitroban or nafazatrom or naxaprostene or octimibate or oxagrelate or pamicogrel or pamicogrel or pentosan-polysulfate or pentoxifylline or picotamide or piracetam or plafibride or prasugrel or prostacyclin or rafigrelide or regrelor or samixogrel or sarpogrelate or satigrel or selatogrel or sulfinpyrazone or taprostene or taprostene or temanogrel or terbogrel or terutroban or ticagrelor or ticlopidine or treprostinil or triflusal or trombodipine).ab,hw,ti.	40,334

#	Query	Results from 22 Feb 2024
4	(annexin* or calphobindin or dianexin or lipocortin or synexin or antistasin or apixaban or betrixaban or darexaban or edoxaban or eribaxaban or fidexaban or letaxaban or otamixaban or razaxaban or rivaroxaban or tanogitran or yagin or abelacimab or asundexian or clavatadine or fasxiator or fesomersen or frunexian or gruticibart or milvexian or osocimab or garadacimab or pegnivacogin or caplacizumab or thrombomodulin or sothrombomodulin or thrombomodulin or argatroban or atecegatran or bivalirudin or bothrojaracin or desulfatohirudin or dextro-phenylalanylprolylargininal or dysinosin or efegatran or flovagatran or hirudin or hirugen or inogatran or lepirudin or melagatran or piperidide or napsagatran or odiparcil or pegmusirudin or pegmusirudin or sofigatran or tanogitran or ximelagatran or thrombomodulin or acenocoumarolor or brodifacoum or bromadiolone or cloricromen or coumafosor or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or phenprocoumon or phepromaron or tioclomarol or warfarin or dociparstat or hirudoid or roneparstat or suleparoide or adomiparin or antixarin or ardeparin or bemiparin or certoparin or dalteparin or danaparoid or deligoparin or embolex or enoxaparin or fondaparinux or idrabiotaparinux or idraparinux or nadroparin or necuparanib or parnaparin or reviparin or semuloparin or sevuparin or tedelparin or tinzaparin).ab,hw,ti.	13,437
5	(abciximab or albolabrin or arginylglycylaspartylserine or bitistatin or carafiban or contortrostatin or disintegrin or echistatin or elarofibanor eptifibatide or fradafiban or gantofiban or kistrin or lamifiban or lefradafiban or lotrafiban or cyclohexylalaninamide or orbofiban or roxifiban or sibrafiban or tadocizumab or tirofiban or triflavin or trigramin or xemilofiban or zalunfiban or vorapaxar).ab,hw,ti.	1,793
6	or/2-5	60,850
7	1 and 6	16

Embase via Ovid (1974+):

#	Query	Results from 22 Feb 2024
1	exp Dengue virus/ or exp dengue/	37,477
2	(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) adj1 fever)).ab,kf,ti,dq.	36,812
3	or/1-2	43,050
4	emergency ward/ or hospital emergency service/ or emergency physician/ or emergency medicine/ or (((emergency or A-and-E or A-E or AE or A&E or A-&-E) adj2 (department* or medicine or room* or unit* or ward*)) or urgent-care or emergicent*).ab,kf,ti,dq,ox,hw,jx. or (ED or ER).ti.	426,612
5	exp anticoagulant agent/ or antithrombocytic agent/ or anticoagulant therapy/	821,182
6	(anticoagula* or anti-coagula* or antithromb* or anti-thromb* or thrombin-inhibit* or ((platelet* or thromb* or coagulat* or clot* or factor or glycoprotein) adj1 (inhibit* or antagonist* or block*)) or antiaggregant* or anti-aggregant* or antiplatelet* or anti-platelet* or DAPT).ab,kf,ti,dq,dy,tn.	462,187
7	(anisindione or anpocogin or antivitamin-K or anti-vitamin-K or apolate-sodium or beciparcil or chlorophacinone or citrate-trisodium or coumarin or defibrotide or dextran-sulfate or diphenadione or fluindione or ghilanten or glycerophosphoinositol-inositolphosphodiesterase or glycosaminoglycan-polysulfate or heparin* or iliparcil or inclacumab or mopidamol or naroparcil or phenindione or tecarfarin or torapsel or tretoquinol or uproleselan or acetylsalicylic-acid or pseudoephedrine or ajoene or aloxiprin or alprostadil-alfadex or anagrelide or ancrod or applaggin or aprosulate or aspirin or ataprost or atopaxar or beraprost or buflomedil-pyridoxal-phosphate or cangrelor or caplacizumab or cicaprost or cilostazol or ciprostene or clopidogrel or cryptolepine or dazoxiben or dehydrocilostazol or dermatan or dextran or dipyridamole or elinogrel or enfenamic-acid or esuberaprost or glenzocimab or heparan-sulfate or ifetroban or iloprost or imolamine or indobufen or isbogrel or itazigrel or linotroban or lixazinone or mipitroban or nafazatrom or naxaprostene or octimibate or oxagrelate or pamicogrel or pamicogrel or pentosan-polysulfate or pentoxifylline or picotamide or piracetam or plafibride or prasugrel or prostacyclin or rafigrelide or regrelor or samixogrel or sarpogrelate or satigrel or selatogrel or sulfinpyrazone or taprostene or taprostene or temanogrel or terbogrel or terutroban or ticagrelor or ticlopidine or treprostinil or triflusal or trombodipine).ab,kf,ti,dq,dy,tn.	688,506

#	Query	Results from 22 Feb 2024
8	(annexin* or calphobindin or dianexin or lipocortin or synexin or antistasin or apixaban or betrixaban or darexaban or edoxaban or eribaxaban or fidexaban or letaxaban or otamixaban or razaxaban or rivaroxaban or tanogitran or yagin or abelacimab or asundexian or clavatadine or fasxiator or fesomersen or frunexian or gruticibart or milvexian or osocimab or garadacimab or pegnivacogin or caplacizumab or thrombomodulin or sothrombomodulin or thrombomodulin or argatroban or atecegatran or bivalirudin or bothrojaracin or desulfatohirudin or dextro-phenylalanylprolylargininal or dysinosin or efegatran or flovagatran or hirudin or hirugen or inogatran or lepirudin or melagatran or piperidide or napsagatran or odiparcil or pegmusirudin or pegmusirudin or sofigatran or tanogitran or ximelagatran or thrombomodulin or acenocoumarolor or brodifacoum or bromadiolone or cloricromen or coumafosor or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or phenprocoumon or phepromaron or tioclomarol or warfarin or dociparstat or hirudoid or roneparstat or suleparoide or adomiparin or antixarin or ardeparin or bemiparin or certoparin or dalteparin or danaparoid or deligoparin or embolex or enoxaparin or fondaparinux or idrabiotaparinux or idraparinux or nadroparin or necuparanib or parnaparin or reviparin or semuloparin or sevuparin or tedelparin or tinzaparin).ab,kf,ti,dq,dy,tn.	257,463
9	(abciximab or albolabrin or arginylglycylaspartylserine or bitistatin or carafiban or contortrostatin or disintegrin or echistatin or elarofibanor eptifibatide or fradafiban or gantofiban or kistrin or lamifiban or lefradafiban or lotrafiban or cyclohexylalaninamide or orbofiban or roxifiban or sibrafiban or tadocizumab or tirofiban or triflavin or trigramin or xemilofiban or zalunfiban or vorapaxar).ab,kf,ti,dq,dy,tn.	25,600
10	or/5-9	1,122,702
11	3 and 4 and 10	25
12	limit 11 to (english or portuguese or spanish)	24
13	limit 12 to conference abstract	9
14	12 not 13	15

International Clinical Trials Registry Platform (ICTRP) from the World Health Organization (2005+) – *standard interface*:

dengue AND (anticoag* OR antithromb* OR clotting-inhibitor OR platelet-inhibitor OR antiplatelet* OR (thrombocyte AND inhibitor) OR heparin OR hirudin OR coumadin OR warfarin OR aspirin)

MEDLINE via Ovid (1946+ and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily):

#	Query	Results from 22 Feb 2024
1	exp Dengue/ or Dengue Virus/	19,848
2	(Dengue or DENV or ((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) adj1 fever)).ab,kf,ti.	29,172
3	or/1-2	30,211
4	Emergency Service, Hospital/ or Emergency Medicine/ or (((emergency or A-and-E or A-E or AE or A&E or A-&-E) adj2 (department* or medicine or room* or unit* or ward*)) or urgent-care or emergicent*).ab,kf,ti,hw,jw. or (ED or ER).ti.	264,091
5	exp Anticoagulants/ or Platelet Aggregation Inhibitors/	278,076
6	(anticoagula* or anti-coagula* or antithromb* or anti-thromb* or thrombin-inhibit* or ((platelet* or thromb* or coagulat* or clot* or fibrinogen or factor or glycoprotein) adj1 (inhibit* or antagonist* or block*)) or antiaggregant* or anti-aggregant* or antiplatelet* or anti-platelet* or DAPT).ab,kf,ti,nm.	258,084

#	Query	Results from 22 Feb 2024
7	(anisindione or anpocogin or antivitamin-K or anti-vitamin-K or apolate-sodium or beciparcil or chlorophacinone or citrate-trisodium or coumarin or defibrotide or dextran-sulfate or diphenadione or fluindione or ghilanten or glycerophosphoinositol-inositolphosphodiesterase or glycosaminoglycan-polysulfate or heparin* or iliparcil or inclacumab or mopidamol or naroparcil or phenindione or tecarfarin or torapsel or tretoquinol or uproleselan or acetylsalicylic-acid or pseudoephedrine or ajoene or aloxiprin or alprostadil-alfadex or anagrelide or ancrod or applaggin or aprosulate or aspirin or ataprost or atopaxar or beraprost or buflomedil-pyridoxal-phosphate or cangrelor or caplacizumab or cicaprost or cilostazol or ciprostene or clopidogrel or cryptolepine or dazoxiben or dehydrocilostazol or dermatan or dextran or dipyridamole or elinogrel or enfenamic-acid or esuberaprost or glenzocimab or heparan-sulfate or ifetroban or iloprost or imolamine or indobufen or isbogrel or itazigrel or linotroban or lixazinone or mipitroban or nafazatrom or naxaprostene or octimibate or oxagrelate or pamicogrel or pamicogrel or pentosan-polysulfate or pentoxifylline or picotamide or piracetam or plafibride or prasugrel or prostacyclin or rafigrelide or regrelor or samixogrel or sarpogrelate or satigrel or selatogrel or sulfinpyrazone or taprostene or taprostene or temanogrel or terbogrel or terutroban or ticagrelor or ticlopidine or treprostinil or triflusal or trombodipine).ab,kf,ti,nm.	306,108
8	(annexin* or calphobindin or dianexin or lipocortin or synexin or antistasin or apixaban or betrixaban or darexaban or edoxaban or eribaxaban or fidexaban or letaxaban or otamixaban or razaxaban or rivaroxaban or tanogitran or yagin or abelacimab or asundexian or clavatadine or fasxiator or fesomersen or frunexian or gruticibart or milvexian or osocimab or garadacimab or pegnivacogin or caplacizumab or thrombomodulin or sothrombomodulin or thrombomodulin or argatroban or atecegatran or bivalirudin or bothrojaracin or desulfatohirudin or dextro-phenylalanylprolylargininal or dysinosin or efegatran or flovagatran or hirudin or hirugen or inogatran or lepirudin or melagatran or piperidide or napsagatran or odiparcil or pegmusirudin or pegmusirudin or sofigatran or tanogitran or ximelagatran or thrombomodulin or acenocoumarolor or brodifacoum or bromadiolone or cloricromen or coumafosor or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or phenprocoumon or phepromaron or tioclomarol or warfarin or dociparstat or hirudoid or roneparstat or suleparoide or adomiparin or antixarin or ardeparin or bemiparin or certoparin or dalteparin or danaparoid or deligoparin or embolex or enoxaparin or fondaparinux or idrabiotaparinux or idraparinux or nadroparin or necuparanib or parnaparin or reviparin or semuloparin or sevuparin or tedelparin or tinzaparin).ab,kf,ti,nm.	98,328
9	(abciximab or albolabrin or arginylglycylaspartylserine or bitistatin or carafiban or contortrostatin or disintegrin or echistatin or elarofibanor eptifibatide or fradafiban or gantofiban or kistrin or lamifiban or lefradafiban or lotrafiban or cyclohexylalaninamide or orbofiban or roxifiban or sibrafiban or tadocizumab or tirofiban or triflavin or trigramin or xemilofiban or zalunfiban or vorapaxar).ab,kf,ti,nm.	10,653
10	or/5-9	614,013
11	3 and 4 and 10	3
12	limit 11 to (english or portuguese or spanish)	3

SciELO via Clarivate (2002+)

#8	#1 AND #2 AND #7
#7	#3 OR #4 OR #5 OR #6
#6	TS=(abciximab or albolabrin or arginylglycylaspartylserine or bitistatin or carafiban or contortrostatin or disintegrin or echistatin or elarofibanor eptifibatide or fradafiban or gantofiban or kistrin or lamifiban or lefradafiban or lotrafiban or cyclohexylalaninamide or orbofiban or roxifiban or sibrafiban or tadocizumab or tirofiban or triflavin or trigramin or xemilofiban or zalunfiban or vorapaxar)
#5	TS=(annexin* or calphobindin or dianexin or lipocortin or synexin or antistasin or apixaban or betrixaban or darexaban or edoxaban or eribaxaban or fidexaban or letaxaban or otamixaban or razaxaban or rivaroxaban or tanogitran or yagin or abelacimab or asundexian or clavatadine or fasxiator or fesomersen or frunexian or gruticibart or milvexian or osocimab or garadacimab or pegnivacogin or caplacizumab or thrombomodulin or sothrombomodulin or thrombomodulin or argatroban or atecegatran or bivalirudin or bothrojaracin or bothrojaracin or desulfatohirudin or dextro-phenylalanylprolylargininal or dysinosin or efegatran or flovagatran or hirudin or hirugen or inogatran or lepirudin or melagatran or piperidide or napsagatran or odiparcil or pegmusirudin or pegmusirudin or sofigatran or tanogitran or ximelagatran or thrombomodulin or acenocoumarolor or brodifacoum or bromadiolone or cloricromen or coumafosor or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or phenprocoumon or phepromaron or tioclomarol or warfarin or dociparstat or hirudoid or roneparstat or suleparoide or adomiparin or antixarin or ardeparin or bemiparin or certoparin or dalteparin or danaparoid or deligoparin or embolex or enoxaparin or fondaparinux or idrabiotaparinux or idraparinux or nadroparin or necuparanib or parnaparin or reviparin or semuloparin or sevuparin or tedelparin or tinzaparin)

#4	TS=(anisindione or anpocogin or antivitamina-K or anti-vitamina-K or apolate-sodio or beciparcil or chlorophacinone or citrate-trisodi* or coumarin or cumarina or defibrotide or dextran-sulfat* or diphenadione or fluindione or ghilanten or glycerophosphoinositol-inositolphosphodiesterase or glycosaminoglycan-polysulfate or heparin* or iliparcil or inclacumab or mopidamol or naroparcil or phenindione or tecarfarin or torapsel or tretoquinol or uproleselan or acetylsalicylic-acid or pseudoephedrine or ajoene or aloxiprin or alprostadil-alfadex or anagrelide or ancrod or applaggin or aprosulate or aspirin* or ataprost or atopaxar or beraprost or buflomedil-pyridoxal-phosphate or cangrelor or caplacizumab or cicaprost or cilostazol or ciprostene or clopidogrel or cryptolepine or dazoxiben or dehydrocilostazol or dermatan or dextran or dipyridamole or elinogrel or enfenamic-acid or esuberaprost or glenzocimab or heparan-sulfate or ifetroban or iloprost or imolamine or indobufen or isbogrel or itazigrel or linotroban or lixazinone or mipitroban or nafazatrom or naxaprostene or octimibate or oxagrelate or pamicogrel or pamicogrel or pentosan-polysulfate or pentoxifylline or picotamide or piracetam or plafibride or prasugrel or prostacyclin or rafigrelide or regrelor or samixogrel or sarpogrelate or satigrel or selatogrel or sulfinpyrazone or taprostene or taprostene or temanogrel or terbogrel or terutroban or ticagrelor or ticlopidine or treprostinil or triflusal or trombodipine)
#3	((TS=((anticoagula* or anti-coagula* or antithromb* or anti-thromb* or antiaggregant* or anti-aggregant* or antiagregante* or anti-agregante* or antiplatelet* or anti-platelet* or antiplaquetario* or DAPT))) OR TS=((trombin* NEAR/1 inhibi*))) OR TS=((platelet* or plaqueta* or thromb* or trombin* or coagulat* or clot* or coágul* or fibrinogen* or factor* or fator or glycoprotein or glicoproteina*) NEAR/1 (inhibi* or antagonist* or block* or bloquea*))
#2	TS=(emergenc*) OR SO=(emergenc*)
#1	TS=(Dengue)

Scopus via Elsevier (1788+):

((TITLE-ABS-KEY (dengue OR denv) OR TITLE-ABS-KEY ((aden OR bouquet OR break-bone OR breakbone OR dandy OR solar OR sun OR bangkok OR thai OR philippine* OR filipin* OR singapore*) W/1 fever))) AND ((TITLE-ABS-KEY ((emergency OR a-and-e OR a-e OR ae OR a&e OR a-&-e) W/2 (department* OR medicine OR room* OR unit* OR ward*)) OR TITLE-ABS-KEY (urgent-care OR emergicent*) OR TITLE (ed OR er) AND SRCTITLE (emergency))) AND (((TITLE-ABS-KEY ((anticoagula* OR anti-coagula* OR antithromb* OR anti-thromb* OR antiaggregant* OR anti-aggregant* OR antiplatelet* OR anti-platelet* OR dapt)) OR TITLE-ABS-KEY (thrombin* W/1 inhibi*) OR TITLE-ABS-KEY ((platelet* OR thromb* OR coagulat* OR clot* OR fibrinogen* OR factor OR glycoprotein) W/1 (inhibi* OR antagonist* OR block*)))) OR (TITLE-ABS-KEY (anisindione OR anpocogin OR antivitamin-k OR anti-vitamin-k OR apolate-sodium OR beciparcil OR chlorophacinone OR citrate-trisodium OR coumarin OR defibrotide OR dextran-sulfate OR diphenadione OR fluindione OR ghilanten OR glycerophosphoinositol-inositolphosphodiesterase OR glycosaminoglycan-polysulfate OR heparin* OR iliparcil OR inclacumab OR mopidamol OR naroparcil OR phenindione OR tecarfarin OR torapsel OR tretoquinol OR uproleselan OR acetylsalicylic-acid OR pseudoephedrine OR ajoene OR aloxiprin OR alprostadil-alfadex OR anagrelide OR ancrod OR applaggin OR aprosulate OR aspirin OR ataprost OR atopaxar OR beraprost OR buflomedil-pyridoxal-phosphate OR cangrelor OR caplacizumab OR cicaprost OR cilostazol OR ciprostene OR clopidogrel OR cryptolepine OR dazoxiben OR dehydrocilostazol OR dermatan OR dextran OR dipyridamole OR elinogrel OR enfenamic-acid OR esuberaprost OR glenzocimab OR heparan-sulfate OR ifetroban OR iloprost OR imolamine OR indobufen OR isbogrel OR itazigrel OR linotroban OR lixazinone OR mipitroban OR nafazatrom OR naxaprostene OR octimibate OR oxagrelate OR pamicogrel OR pamicogrel OR pentosan-polysulfate OR pentoxifylline OR picotamide OR piracetam OR plafibride OR prasugrel OR prostacyclin OR rafigrelide OR regrelor OR samixogrel OR sarpogrelate OR satigrel OR selatogrel OR sulfinpyrazone OR taprostene OR taprostene OR temanogrel OR terbogrel OR terutroban OR ticagrelor OR ticlopidine OR treprostinil OR triflusal OR trombodipine)) OR (TITLE-ABS-KEY (annexin* OR calphobindin OR dianexin OR lipocortin OR synexin OR antistasin OR apixaban OR betrixaban OR darexaban OR edoxaban OR eribaxaban OR fidexaban OR letaxaban OR otamixaban OR razaxaban OR rivaroxaban OR tanogitran OR yagin OR abelacimab OR asundexian OR clavatadine OR fasxiator OR fesomersen OR frunexian OR gruticibart OR milvexian OR osocimab OR garadacimab OR pegnivacogin OR caplacizumab OR thrombomodulin OR sothrombomodulin OR thrombomodulin OR argatroban OR atecegatran OR bivalirudin OR bothrojaracin OR desulfatohirudin OR dextro-phenylalanylprolylargininal OR dysinosin OR efegatran OR flovagatran OR hirudin OR hirugen OR inogatran OR lepirudin OR melagatran OR piperidide OR napsagatran OR odiparcil OR pegmusirudin OR pegmusirudin OR sofigatran

OR tanogitran OR ximelagatran OR thrombomodulin OR acenocoumarolor OR brodifacoum OR bromadiolone OR cloricromen OR coumafosor OR coumatetralyl OR coumetarol OR dicoumarol OR difenacoum OR ethyl-biscoumacetate OR flocoumafen OR galbanic-acid OR phenprocoumon OR phepromaron OR tioclomarol OR warfarin OR dociparstat OR hirudoid OR roneparstat OR suleparoide OR adomiparin OR antixarin OR ardeparin OR bemiparin OR certoparin OR dalteparin OR danaparoid OR deligoparin OR embolex OR enoxaparin OR fondaparinux OR idrabiotaparinux OR idraparinux OR nadroparin OR necuparanib OR parnaparin OR reviparin OR semuloparin OR sevuparin OR tedelparin OR tinzaparin)) OR (TITLE-ABS-KEY (abciximab OR albolabrin OR arginylglycylaspartylserine OR bitistatin OR carafiban OR contortrostatin OR disintegrin OR echistatin OR elarofibanor AND eptifibatide OR fradafiban OR gantofiban OR kistrin OR lamifiban OR lefradafiban OR lotrafiban OR cyclohexylalaninamide OR orbofiban OR roxifiban OR sibrafiban OR tadocizumab OR tirofiban OR triflavin OR trigramin OR xemilofiban OR zalunfiban OR vorapaxar)))

Web of Science Core Collection via Clarivate Analytics (Science Citation Index Expanded 1975+ & Emerging Sources Citation Index 2015+):

#8	#1 AND #2 AND #7
#7	#3 OR #4 OR #5 OR #6
#6	TS=(abciximab or albolabrin or arginylglycylaspartylserine or bitistatin or carafiban or contortrostatin or disintegrin or echistatin or elarofibanor eptifibatide or fradafiban or gantofiban or kistrin or lamifiban or lefradafiban or lotrafiban or cyclohexylalaninamide or orbofiban or roxifiban or sibrafiban or tadocizumab or tirofiban or triflavin or trigramin or xemilofiban or zalunfiban or vorapaxar)
#5	TS=(annexin* or calphobindin or dianexin or lipocortin or synexin or antistasin or apixaban or betrixaban or darexaban or edoxaban or eribaxaban or fidexaban or letaxaban or otamixaban or razaxaban or rivaroxaban or tanogitran or yagin or abelacimab or asundexian or clavatadine or fasxiator or fesomersen or frunexian or gruticibart or milvexian or osocimab or garadacimab or pegnivacogin or caplacizumab or thrombomodulin or sothrombomodulin or thrombomodulin or argatroban or atecegatran or bivalirudin or bothrojaracin or desulfatohirudin or dextro-phenylalanylprolylargininal or dysinosin or efegatran or flovagatran or hirudin or hirugen or inogatran or lepirudin or melagatran or piperidide or napsagatran or odiparcil or pegmusirudin or pegmusirudin or sofigatran or tanogitran or ximelagatran or thrombomodulin or acenocoumarolor or brodifacoum or bromadiolone or cloricromen or coumafosor or coumatetralyl or coumetarol or dicoumarol or difenacoum or ethyl-biscoumacetate or flocoumafen or galbanic-acid or phenprocoumon or phepromaron or tioclomarol or warfarin or dociparstat or hirudoid or roneparstat or suleparoide or adomiparin or antixarin or ardeparin or bemiparin or certoparin or dalteparin or danaparoid or deligoparin or embolex or enoxaparin or fondaparinux or idrabiotaparinux or idraparinux or nadroparin or necuparanib or parnaparin or reviparin or semuloparin or sevuparin or tedelparin or tinzaparin)
#4	TS=(anisindione or anpocogin or antivitamin-K or anti-vitamin-K or apolate-sodium or beciparcil or chlorophacinone or citrate-trisodium or coumarin or defibrotide or dextran-sulfate or diphenadione or fluindione or ghilanten or glycerophosphoinositol-inositolphosphodiesterase or glycosaminoglycan-polysulfate or heparin* or iliparcil or inclacumab or mopidamol or naroparcil or phenindione or tecarfarin or torapsel or tretoquinol or uproleselan or acetylsalicylic-acid or pseudoephedrine or ajoene or aloxiprin or alprostadil-alfadex or anagrelide or ancrod or applaggin or aprosulate or aspirin or ataprost or atopaxar or beraprost or buflomedil-pyridoxal-phosphate or cangrelor or caplacizumab or cicaprost or cilostazol or ciprostene or clopidogrel or cryptolepine or dazoxiben or dehydrocilostazol or dermatan or dextran or dipyridamole or elinogrel or enfenamic-acid or esuberaprost or glenzocimab or heparan-sulfate or ifetroban or iloprost or imolamine or indobufen or isbogrel or itazigrel or linotroban or lixazinone or mipitroban or nafazatrom or naxaprostene or octimibate or oxagrelate or pamicogrel or pamicogrel or pentosan-polysulfate or pentoxifylline or picotamide or piracetam or plafibride or prasugrel or prostacyclin or rafigrelide or regrelor or samixogrel or sarpogrelate or satigrel or selatogrel or sulfinpyrazone or taprostene or taprostene or temanogrel or terbogrel or terutroban or ticagrelor or ticlopidine or treprostinil or triflusal or trombodipine)
#3	(TS=(anticoagula* or anti-coagula* or antithromb* or anti-thromb* or thrombin-inhibit* or antiaggregant* or anti-aggregant* or antiplatelet* or anti-platelet* or DAPT)) OR TS=(((platelet* or thromb* or coagulat* or clot* or factor or glycoprotein) NEAR/1 (inhibit* or antagonist* or block*)))
#2	TS=((emergency or A-and-E or A-E or A&E or A-&-E) NEAR/2 (department* or medicine or room* or unit* or ward*)) OR TS=(urgent-care or emergicent*) OR TI=(ED or ER) OR SO=(emergency)
#1	TS=(Dengue or DENV) or TS=((Aden or bouquet or break-bone or breakbone or dandy or solar or sun or Bangkok or Thai or Philippine* or Filipin* or Singapore*) NEAR/1 fever)