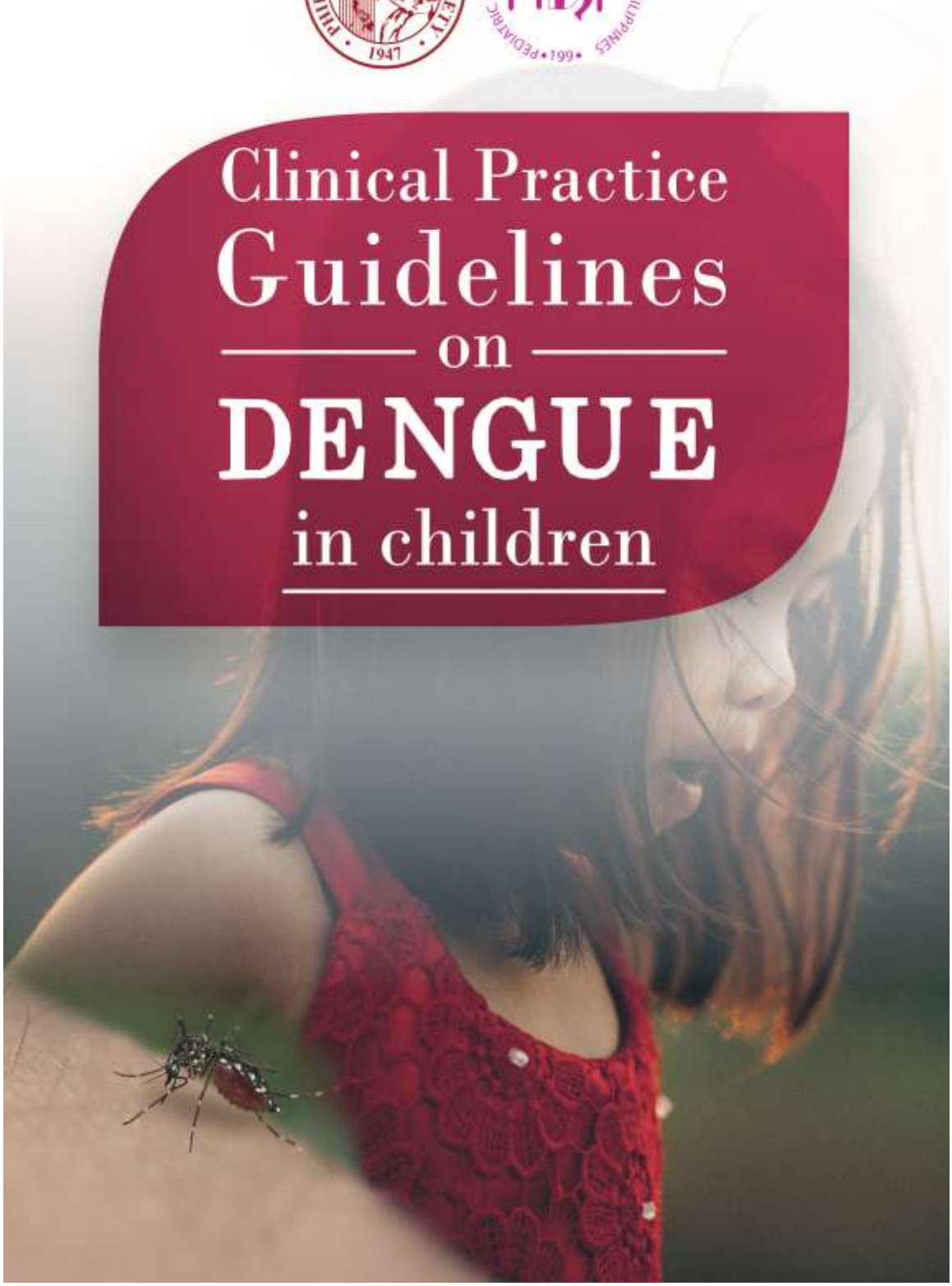

Clinical Practice Guidelines on DENGUE in children

CLINICAL PRACTICE GUIDELINES ON DENGUE IN CHILDREN

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Integrated Midwives Association of the Philippines (IMAP)

Lions Club International

Philippine Ambulatory Pediatric Association (PAPA)

Philippine Private School Health Officers Association (PSHOA)

Philippine Society of Critical Care Medicine, Inc. (PSCCM)

Society of Adolescent Medicine of the Philippines, Inc. (SAMPI)

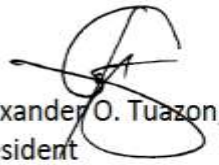
Society of Pediatric Critical Care Medicine, Philippines (SPCCMP)

MESSAGE

We welcome the new Clinical Practice Guideline on Dengue spearheaded by the Pediatric Infectious Disease Society of the Philippines (PIDSP) through the leadership of the Dengue CPG Steering Committee chaired by Dr. Jaime Santos, co-chaired by Dr. Ma. Liza Antoinette Gonzales, the current President of PIDSP, and its members Dr. Mary Antonette Madrid and Dr. Rosario Capeding. This very important effort has been supported by a group of eminent contributors and has been vetted by stakeholders.

From 1953, when the first epidemic of dengue hemorrhagic fever recorded in the world occurred in Manila, dengue has progressively evolved into a significant cause of hospitalization and death among our children. It has now become practically endemic, reported in all regions of the country and last year, 2016, dengue accounted for more than 400 deaths. It has become imperative that as pediatricians charged with the care of our country's children, we must constantly arm ourselves with the best possible knowledge and skills to deal with this alarming scourge. To this need, PIDSP has taken the leadership through this new clinical practice guideline in providing the best and current evidence-based practices in managing dengue.

My heartfelt appreciation to PIDSP, the Dengue Clinical Practice Guideline working groups and all who provided support to make this possible. This CPG will be a most helpful clinical practice tool.



Alexander O. Tuazon, MD, MDE
President
Philippine Pediatric Society, Inc.

FOREWORD

Dengue is now considered to be the most important, most rapidly spreading mosquito-borne viral disease in the world. The burden of dengue has made this disease a major public health concern globally, particularly in tropical and subtropical countries, resulting in substantial economic burden**.**

This current CPG on dengue developed by the Pediatric Infectious Disease Society (PIDSP) Dengue Clinical Practice Guideline group with partial support from the Philippine Pediatric Society (PPS), is an update of the Evidence-based Guidelines on DF/DHF that was published by the PPS in 2008. It focuses on specific questions considered to be priorities based on relevance, inconsistencies and controversies in available evidence. The practice guideline was prepared by a panel of multidisciplinary specialists based on the review and summary of existing evidence. It provides recommendations on the clinical signs and laboratory findings that would predict outcome, optimal fluid therapy in patients with or without shock, role of blood product transfusion to prevent or treat patients with dengue, and effectiveness of citronella-based insect repellents in preventing dengue.

Due to its limited scope, this guideline does not include recommendations on diagnostic tests and other preventive strategies for which future recommendations will need to be developed. Furthermore, following the recommended process for evidence-based guidelines revealed many key un-answered questions and identified research gaps that will require further studies. Continued follow-up and vigilance with regards to new developments is crucial to ensure that answers will be provided to further strengthen optimal practices in dengue diagnosis, management, prevention and control. In the meantime, we hope that the guiding principles and statements on the specific topics covered in this guideline will help and support practitioners, patients and other stakeholders in deciding on standardized clinical diagnosis and management practices, improve the quality and consistency in healthcare of children with dengue, and promote more efficient use of resources.

Ma. Liza Antoinette M. Gonzales, M.D.
President, Pediatric Infectious Disease Society of the Philippines
Co-Chair, Dengue CPG Oversight Committee

DEFINITION OF KEY TERMS

Dengue Hemorrhagic fever (DHF): characterized by presence of all four criteria: (a) fever or history of fever (acute onset, high and continuous, lasting two to seven days); (b) hemorrhagic manifestations, any one of the following: a positive tourniquet test, petechiae, purpura, ecchymosis, epistaxis, gum bleeding, and hematemesis and/or melena (c) thrombocytopenia (≤ 100 000 cells per cubic mm), and; (d) Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following: hemoconcentration (manifested as increasing hematocrit ≥ 20% above average for age, sex, and population or decreasing hematocrit following volume replacement treatment ≥ 20% of baseline) or signs of plasma leakage, i.e. pleural effusion, ascites and hypoproteinemia

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Dengue shock syndrome (DSS) - The patient is considered to have shock if the pulse pressure (i.e. the difference between the systolic and diastolic pressures) is ≤ 20 mm Hg in children and he/she has signs of poor capillary perfusion (cold extremities, delayed capillary refill, and rapid pulse rate). The two phases of shock are: (a) compensated shock - initial stage of shock wherein compensatory mechanism which maintains a normal systolic blood pressure also produces tachycardia and peripheral vasoconstriction with reduced skin perfusion, resulting in cold extremities and delayed capillary refill time; the diastolic pressure rises towards the systolic pressure and the pulse pressure narrows as the peripheral vascular resistance increases; patients in early dengue shock often remain conscious and lucid; (b) hypotensive (or decompensated) shock – late stage of shock characterized by decompensation and abrupt disappearance of both pressures; prolonged hypotensive shock and hypoxia may lead to multi-organ failure and complicated clinical course

Disseminated intravascular coagulation (DIC) - an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. Laboratory diagnosis of DIC is based on tests that demonstrate activation of coagulation and consumption of clotting factors, coagulation inhibitors, hence, are prolonged and platelets are reduced. It can originate from and cause damage to the microvasculature, which, if sufficiently severe, can produce organ dysfunction. Serial coagulation tests are more helpful than single laboratory determination.

Severe Dengue - defined by one or more of the following: (a) plasma leakage that may lead to shock (dengue shock) and/or fluid accumulation, with or without respiratory distress, and/or (b) severe bleeding, and/or (c) severe organ impairment.

ABBREVIATIONS

ADH	Antidiuretic hormone
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Actual platelet count
aPTT	activated Partial thromboplastin time
AST	Aspartate aminotransferase
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CPG	Clinical practice guideline
DEET	N,N-Diethyl-meta-toluamide
DEM	N,N-Diethyl-D,L-mandelic acid amide
DF	Dengue fever
DHF	Dengue hemorrhagic fever
DIC	Disseminated intravascular coagulopathy
DOH	Department of Health
DMP	Dimethylphthalate
DSS	Dengue shock syndrome
ELISA	Enzyme-linked immunosorbent assay
EPA	Environmental Protection Agency
ER	Emergency room
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FWB	Fresh whole blood
GP	Guideline Panel
Hct	Hematocrit
HES	Hydroxyethyl starch
Hgb	Hemoglobin
HR	Hazard ratio
INR	International normalized ratio
IVF	Intravenous fluid
OC	Oversight Committee
OR	Odds ratio
PCR	Polymerase chain reaction
PIDSP	Pediatric Infectious Disease Society of the Philippines
PIDSR	Philippine Integrated Disease Surveillance and Response
pNa	Plasma sodium
PNSP	Pediatric Nephrology Society of the Philippines
PPS	Philippine Pediatric Society
PRBC	Packed red blood cell
PT	Prothrombin time
PTT	Partial thromboplastin time

RCT	Randomized controlled trial
RR	Relative risk
RT-PCR	Reverse transcriptase-polymerase chain reaction
SEARO	South East Asia Regional Office
SINAN	National Notifiable Disease Surveillance System
TRC	Technical Review Committee
WBC	White blood cell
WHO	World Health Organization
WMD	Weight mean difference

EXECUTIVE SUMMARY

2017 PPS-PIDSP CLINICAL PRACTICE GUIDELINES ON DENGUE

Current World Health Organization estimates show that 50 to 100 million new dengue infections occur yearly. In affected regions such as Asia and Latin America, severe dengue is a leading cause of hospitalization and mortality particularly in children. While there is no specific treatment for dengue, prompt recognition and timely intervention affects prognosis.

This current evidence-based guideline updates the recommendations contained in the PPS 2008 Practice Guidelines on DF/DHF answering relevant questions in the care of a child with dengue illness. The intended users of this document include primary care physicians, family medicine physicians, pediatricians, and other healthcare workers involved in the diagnosis and management of dengue in children.

The eight priority questions identified and corresponding recommendations were developed by a 16-member group of experts composed of an Oversight Committee, a Guideline Writing Panel and a Technical Review Committee. Quality and strength of evidence was rated using the GRADE methodology. Draft recommendations presented in the table below were finalized after these were presented to and voted on by the members of the Stakeholders Panel.

No.	Recommendation	Strength of Recommendation	Quality of Evidence
1	***Clinical signs and symptoms that warrant admission***		
	Recommendation 1: Among patients with confirmed or presumptive diagnosis of dengue in the outpatient setting, patients with the following signs and symptoms should be admitted in a healthcare facility for closer monitoring and observation: • Shortness of breath • Irritability or drowsiness • Pleural effusion • Abdominal pain • Melena • Elevated hematocrit • Decreased or decreasing platelet count	Strong	Low and Very low
	Recommendation 2**:** Among patients with confirmed or presumptive diagnosis of dengue in the outpatient setting, there is insufficient evidence to say that vomiting is associated with more severe dengue. However, because patients with vomiting cannot tolerate oral rehydration fluids, consider admission	Strong	Very low

2	***Risk factors that are associated with mortality*** ***Recommendation 1*:** Patients with dengue who present with any one of the following clinical findings may be at increased risk for mortality. • Hypotension on admission • Narrow pulse pressure on admission • DHF stage 3 and 4 (severe dengue) • History of previous dengue • Prolonged shock • Respiratory failure • Liver failure (AST elevation > 200 u and INR > 1.3) • Renal failure (BUN >20 mg% and serum Creatinine >1.0mg %) • Significant bleeding including gastrointestinal bleeding • Severe plasma leakage in multiple sites (pleural effusion, pericardial effusion and ascites)	Strong	Moderate, low and very low
	***Recommendation 2*:** The presence of two or more of the following warning signs in patients with dengue may increase the risk for mortality: • severe abdominal pain • arterial hypotension • neurologic manifestation • painful hepatomegaly • hypovolemic shock • liver failure • myocarditis	Strong	Very low
	Recommendation 3: Patients with dengue who present with one or more of the following laboratory findings may be at increased risk for mortality and warrant hospital admission for close monitoring • Decline in Hgb by $\geq$ 20% • Thrombocytopenia, with APC $\leq$ 50,000/mm^3 • Hemoconcentration, with Hct > 40 % or 20% increase in lowest and highest hematocrit • Creatinine > 1 mg % • AST > 1000 u • Acidosis	Strong	Moderate, low and very low
	***Recommendation 4*:** Prothrombin time (PT) and Partial Prothrombin Time (PTT) do not differentiate those who may be at increased risk for mortality and are not recommended as routine tests for patients with dengue	Strong	Low
3	***Clinical signs and/or laboratory findings that indicate significant bleeding*** ***Recommendation 1*:** Among patients admitted because of dengue, the presence of one or more	Strong	Low to very low

	of the following clinical or laboratory findings may increase the risk of bleeding • Hypotension • Narrow pulse pressure • Platelet count < 50,000/mm^3 • WBC count < 5000/mm^3 • Hepatomegaly • Elevated ALT (> 3x the normal value)		
	Recommendation 2: Among patients admitted because of dengue, there is some evidence to suggest that the following signs and symptoms may be associated with significant bleeding. • Vomiting • Abdominal pain • Restlessness • Pleural effusion or ascites • Rash ***Recommendation 3***: Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) were not shown to be significantly associated with bleeding and should not be routinely done in patient with dengue.	Strong Strong	Low to very low Very low
4	***Isotonic compared to hypotonic IVFs in reducing mortality among dengue patients without shock*** ***Recommendation:*** • There is insufficient evidence that the tonicity of the intravenous fluid has an effect on mortality in dengue patients without shock. • Isotonic fluids can be used as maintenance for dengue patients without shock. • The use of hypotonic IVF is associated with hyponatremia among hospitalized pediatric patients.	Strong	Low
5	***Colloids compared to crystalloids in reducing mortality among dengue patients with shock*** ***Recommendation*:** • In dengue patients with shock, either crystalloids or colloids may be used for fluid resuscitation. • There is insufficient evidence to say that the use of colloid IVF compared to crystalloids will have an effect on mortality. • The use of colloids may be associated with more adverse reactions (e.g. bleeding, allergic reactions) compared to crystalloids.	Strong	Low and very low
6	***Prophylactic platelet transfusion in improving platelet count, preventing hemorrhage and reducing mortality among patients with thrombocytopenia because of dengue***		

	***Recommendation*:** • There is insufficient evidence to say that prophylactic platelet transfusion in patients with minimal or no active bleeding will improve platelet counts, prevent hemorrhage and reduce mortality. • Children with dengue who have platelet count <50,000/mm^3 with minimal or no active bleeding should not be given prophylactic platelet transfusion.	Strong	Moderate to very low
7	***Plasma transfusion in controlling bleeding and reducing mortality among dengue patients with significant bleeding*** ***Recommendation*:** • Among dengue patients with significant bleeding, there is insufficient evidence that plasma transfusion has an effect on controlling bleeding and reducing mortality. • The effect of plasma transfusion on platelet count recovery is not significant in dengue patients with bleeding. • In children exhibiting signs of disseminated intravascular coagulopathy (DIC), plasma transfusion may be considered.	Strong	Low
8	***Citronella-based repellents compared to DEET-based repellents in reducing the incidence of Dengue*** ***Recommendation*:** There is insufficient evidence to say that use of citronella-based repellents is more effective than DEET-based repellents in reducing dengue transmission.	Strong	Very low

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CHAPTER 1

INTRODUCTION

In recent years, dengue emerged to become the most significant vector-borne viral disease of public health importance particularly in the tropical and subtropical countries. It is estimated that 390 million dengue infections occur per year, of which 96 million develop clinically apparent disease (Bhatt, 2013). The disease can be fatal without prompt intervention.

In the year 2014, there were a total of 121,580 reported dengue cases nationwide based on Philippine Integrated Disease Surveillance and Response (PIDSR) data, with 465 deaths giving a case fatality rate of 0.38% (PIDSR, 2014). A recent local study showed that the economic burden of dengue illness was substantial. With an estimated annual average of 842,867 clinically diagnosed dengue illness, the total annual aggregate cost was $345 million, of which 89.7% was for hospitalized cases and 10.3% for ambulatory cases (Edillo, 2015).

While there is no specific treatment for dengue, early recognition and timely hospitalization affects prognosis. It is therefore important, particularly for primary care physicians, to be provided with guidance on disease identification and appropriate management. Since the release of the PPS 2008 Practice Guidelines on DF/DHF, newer systematic reviews, meta-analyses, and RCTs became available and were utilized in drafting this updated CPG to answer relevant questions in the care of a child with dengue illness.

Practice variation among the different health facilities in terms of clinical diagnosis of dengue based on signs and symptoms, interpretation of laboratory evaluations, criteria for admission, use of fluids and blood and blood component products, and concern on the safety of insect repellents, exists. Thus, there is a need to continue revisiting the guideline.

I. Background

DOH and PPS Guidelines

In 2010, the PPS Committee on Dengue created an Interim Guideline on Fluid Management of DF and DHF which was posted in the Society's website on October 2010 (Philippine Pediatric Society [PPS], 2010). During the same month, the DOH (with support from WHO) held a National Dengue Workshop on Clinical Management, which provided a venue for the creation of DOH Revised Dengue Clinical Management Guidelines 2011 (DOH, 2011). The PPS Interim Guidelines were incorporated in the 2011 document. Subsequently, the PPS Committee on Dengue convened in August 2012 and compared available data from the 2011 DOH Revised Guidelines and the 2011 WHO SEARO Comprehensive Guidelines (WHO 2011) to come up with recommendations on fluid management that was more relevant to use in the local setting. This "Revised Guidelines on Fluid Management of DF and DHF 2012" was also uploaded to the PPS website (PPS 2012).

II. Guideline Objectives:

1. To provide an evidence-based guideline in the recognition and management of dengue illness in children
2. To improve patient outcome through early identification of severe disease and timely intervention of cases that warrant hospitalization

III. Target Users: These guidelines are intended for primary care physicians, family medicine physicians, pediatricians, and other healthcare workers involved in the diagnosis and management of dengue in children

IV. Organization of the Clinical Practice Guideline on Dengue

A. Oversight (Steering) Committee (OC)

The Oversight committee, composed of PIDSP members, was in charge of planning the activities, coordinating with members of the Technical Review Committee (TRC) and convening the multisectoral stakeholders panel who will make the final recommendations. This group was responsible for determining the objectives of the CPG, the target users and planned outcome of developing the CPG.

B. Guideline Writing Panel (GWP)

The GWP is composed of specialists in the field of infectious diseases, hematology, critical care, and epidemiology. They were responsible for writing the summary of evidence, the draft recommendations for presentation to the stakeholders and the final guideline recommendations.

C. Technical Review Committee (TRC)

Literature search, tracking and retrieving the journals, appraisal and summary of evidence, and preparation of the draft recommendations were done by group of epidemiologists from the Asia Pacific Center for Evidence Based Healthcare, Inc.

D. Stakeholders Panel (Voting Consensus Panel)

The expert panel is composed of stakeholders including heads of societies, representatives from academic institutions, and representatives from government and non-government health agencies. The panelists were responsible for reviewing the draft recommendation statements and evidence, and participated in the discussion and voting.

V. Methodology

A. Identifying the guideline questions:

Out of 20 questions initially considered, eight (8) questions were chosen by the Oversight Committee (OC) and the Guideline Panel (GWP) based on the following: (1) relevance, (2) priority and perceived urgency, (3) inconsistency of evidence, and (4) controversies.

This current edition of the Practice Guidelines for Dengue focuses on the following clinical questions:

Question 1: Among patients with confirmed or presumptive diagnosis of Dengue in the outpatient setting, what clinical signs and symptoms warrant admission?

Question 2: Among patients with dengue, which risk factors are associated with mortality?

Question 3: Among patients admitted because of dengue, which clinical signs and/or laboratory findings indicate significant bleeding?

Question 4: Among dengue patients without shock how effective are isotonic IVFs compared to hypotonic IVFs in reducing mortality?

Question 5: Among dengue patients with shock, how effective are colloidal IVFs compared to crystalloid IVFs in reducing mortality?

Question 6: Among patients with thrombocytopenia because of dengue, how effective is prophylactic platelet transfusion in improving platelet count, preventing hemorrhage, and reducing mortality?

Question 7: Among dengue patients with significant bleeding, how effective is plasma transfusion in controlling bleeding and reducing mortality?

Question 8: Among populations at risk for Dengue transmission, how effective are citronella-based repellents compared to DEET-based repellents in reducing the incidence of Dengue?

The use of the dengue vaccine was not tackled because these guidelines were conceptualized before the introduction of the vaccine in the local market. The user is referred to the Pediatric Infectious Disease Society of the Philippines (PIDSP) Statement on the Recommendation for the Use of the Dengue Vaccine accessible through the PIDSP website (http://pidsphil.org/download/RECOMMENDATION-DENGUE-VACCINE-MAY2016.pdf)

B. Search and retrieval of relevant articles

A systematic search of literature was conducted by the TRC using electronic databases and other conventional methods. Medline was searched for relevant articles indexed from 1966 to 24 September 2014 using the terms derived from each of the question. Mesh terms were often used because of its ability to explode. In addition, a local database called Herdin was searched, but since the search engine was not as sophisticated, manual searching was conducted upon obtaining abstracts from a broad topic search. There were no restrictions placed on language, age, or year of publication. Meta-analysis or systematic reviews were retrieved and used when available.

Aside from searching electronic databases, local experts from the Philippine Pediatric Society and the Pediatric Infectious Disease Society of the Philippines were asked for articles that they were aware of whether published or

unpublished. Manual searching of bibliographies from eligible articles were also conducted to identify references missed in the initial search.

C. Grading the quality of evidence and preparation of evidence summaries

The quality of evidence and strength of recommendation was rated using the GRADE methodology (GRADE Working Group, 2004) (see Table 1) by the TRC.

The quality of evidence is defined as the confidence that the reported estimates of effect are adequate to support a specific recommendation. The GRADE system classifies the quality of evidence as high, moderate, low and very low. Randomized controlled trials are initially rated as high-quality evidence but may be downgraded for several reasons, including risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias. Observational studies are initially rated as low-quality evidence but may be upgraded if the magnitude of the treatment effect is very large, if evidence indicates a dose–response relationship or if all plausible biases would underestimate the effect.

Table 1. Quality of Evidence Rating using the Grade Methodology

Quality	Definition
High	Further research is unlikely to change confidence in the estimates of the effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of the effect and may change the estimate
Low	Further research is very likely to have an important impact on the confidence of the effect and is likely to change the estimate
Very Low	Any estimate of effect is very uncertain

Additional categories considered when grading quality of evidence: (1) risk of bias (study limitations); (2) indirectness; (3) inconsistency; (4) imprecision; and (5) publication bias.

Deciding whether an outcome is critical, important but not critical, or not important, is a value judgment that should take account of the value of those who will be affected by adherence to subsequent recommendations[10]. The outcome is considered as critical for a judgment if the risk of the adverse effect is serious and could result in mortality or a life-threatening condition. Other outcomes that are important but not critical are those that are significant but may not necessarily increase the risk for mortality.

D. Preparation of the draft recommendations

The Guideline Writing Panel was tasked with reviewing and evaluating the quality of evidence and the draft recommendations submitted by the TRC. They were also responsible for revising and finalizing the guideline recommendations.

E. Consensus development process

1. Panel of stakeholders

The first evidence based-draft was circulated to the panelists at least 1 week prior to the scheduled en-banc meeting to allow review of the recommendation statements. During the meeting, the members of the GDG presented each recommendation with the supporting evidence. Using the nominal group technique, each recommendation was discussed taking into account not only supporting evidence but also consideration of other criteria:

Table 2. Criteria for Consideration in Recommendation Development

Domain	Rationale
Quality of evidence	Assessment of the degree of confidence in the estimate of the effect
Benefits and Harms (Risks)	Desirable effects (benefits) need to be weighted against harmful or undesirable effects (risks), considering any previous recommendation or another alternative. The larger the gap or gradient in favor of the benefits over the risks, the more likely that a strong recommendation will be made
Values and preferences	Judgment of how much the people affected by the intervention or option value each of the outcomes.
Acceptability	How much an intervention or recommendation is accepted by the people who are affected by it or who are implementing or who are implementing it. If the recommendation is likely to be widely accepted or valued highly, it is likely that a strong recommendation will be made. If there is a great deal of variability or strong reasons that a recommendation is unlikely to be accepted, it is more likely that a weak recommendation will be made.
Feasibility (including resources use consideration)	Whether an intervention is achievable and sustainable in a setting where the greatest impact is expected.

Based on the criteria provided, the panel assessed each recommendation as “strong recommendation”, “weak recommendation” or “no recommendation.” A preliminary vote on every item was obtained. A consensus was arrived at when 75% or more of the votes were obtained from any recommendation.

Table 3. Assessment Criteria for the Strength of Recommendations

Strength of recommendations	Rationale
Strong	The Panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Weak	The Panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects. However, the recommendation is only applicable to a specific group, population or setting OR where new evidence may result in changing the balance of risk to benefit OR where the benefits may not warrant the cost or resource requirements in all settings.
No recommendation	Further research is required before any recommendation can be made.

Any comment, feedback, and discussions that resulted from this meeting were presented to the Guideline Panel for incorporation into the second draft. All issues that were brought up during the stakeholders meeting were resolved by consensus and no further correspondence or voting outside of the meeting was necessary. The second draft will be circulated to the stakeholders panel for further comments and revisions.

2. Public Forum

This revised draft will be presented in a public forum consisting of appropriate stakeholders. Verbal or written feedback regarding the recommendations will be encouraged. After this public forum, the third and final version of the guidelines will be produced.

F. Guideline dissemination

The final version of the guideline will be published as a separate document and will also be accessible through the PIDSP website.

VI. DISCLAIMER

Recommendations are a guide and may not be appropriate for use in all situations. Healthcare providers need to use clinical judgment, knowledge, expertise, and available resources, when deciding whether it is appropriate to apply the recommendations in the guideline.

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CHAPTER 2

CLINICAL AND LABORATORY FEATURES OF DENGUE

In 2009, the World Health Organization (WHO) set up criteria for classifying dengue into levels of severity based on clinical and/or laboratory parameters (WHO 2009). Dengue patients are classified as severe dengue or non-severe dengue, with the group of patients with non-severe dengue subdivided into those with warning signs and those without warning signs.

Dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations (Rigau-Perez 1998). After an incubation period of 3 to 14 days, the illness begins abruptly and is followed by the three phases: febrile, critical and recovery (Yip 1980). The acute febrile phase of dengue usually lasts 2–7 days, often accompanied by generalized body ache, muscle and joint pains, headache, retro-orbital pain, facial flushing, sore throat, hyperemic pharynx, macular or maculopapular rash, petechiae and mild mucosal membrane bleeding (Kalayanarooj 1997; Balmaseda 2005). A positive tourniquet test and progressive decrease in total white cell count are early findings which could differentiate dengue from other acute febrile illnesses (Kalayanarooj 1997; Phuong 2002). These clinical features are indistinguishable between severe and non-severe dengue cases. During fever defervescence, usually on days 3–7 of illness, an increase in capillary permeability in parallel with increasing hematocrit levels may occur, marking the beginning of the critical phase (Srikiatkhachorn 2007; Nimmannitya 1969). The period of clinically significant plasma leakage usually lasts 24–48 hours, followed by a convalescent phase with gradual improvement and stabilization of the hemodynamic status. Warning signs of progression to severe dengue occur in the late febrile phase and include persistent vomiting, severe abdominal pain, mucosal bleeding, difficulty breathing, and early signs of shock. Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage (Kalayanarooj 1997). At this point patients with nonsevere disease begin to improve, but people with clinically significant plasma leakage attributable to increased vascular permeability become worse and develop severe dengue disease with pleural effusion and/or ascites, hypovolemic shock, severe hemorrhage, or organ impairment (WHO 2009). Shock occurs when a critical volume of plasma is lost through leakage and is often preceded by warning signs. With prolonged shock, the consequent organ hypoperfusion results in progressive organ impairment, metabolic acidosis and disseminated intravascular coagulation. This in turn leads to severe hemorrhage causing the hematocrit to decrease in severe shock. Severe organ impairment such as severe hepatitis, encephalitis or myocarditis and/or severe bleeding may also develop without obvious plasma leakage or shock (WHO 2009).

The group progressing from non-severe to severe disease is difficult to define, but this is an important concern since appropriate treatment may prevent these patients from developing more severe clinical conditions. Therefore monitoring for warning signs and other clinical parameters is crucial to recognizing progression to the critical phase. This will enable appropriate treatment with intravenous fluid therapy that may prevent these patients from developing more severe clinical conditions.

Question 1: Among patients with confirmed or presumptive diagnosis of dengue in the outpatient setting, what clinical signs and symptoms warrant admission?

Recommendation 1:
Among patients with confirmed or presumptive diagnosis of dengue in the outpatient setting, patients with the following signs and symptoms should be admitted in a healthcare facility for closer monitoring and observation:

- Shortness of breath
- Irritability or drowsiness
- Pleural effusion
- Abdominal pain
- Melena
- Elevated hematocrit
- Decreased or decreasing platelet count

These signs and symptoms are strongly associated with more severe Dengue infection.
***(Strong recommendation, based on low and very low quality evidence*)**

Recommendation 2:
Among patients with confirmed or presumptive diagnosis of dengue in the outpatient setting, there is insufficient evidence to say that vomiting is associated with more severe dengue. However, because patients with vomiting cannot tolerate oral rehydration fluids, consider admission.
***(Strong recommendation, based on very low quality evidence*)**

Summary of Evidence

A total of nine studies evaluating clinical and laboratory parameters as risk factors for the development of dengue shock syndrome were reviewed, five prospective studies (Araneta 2001; Aseron-Banaga 2003; Chuansumrit 2010; Basurko 2012; Manuel 2005) and four retrospective studies (Farol 2003; Gibson 2013; Gupta 2011; Tantracheewathorn 2007). Three of the four prospective studies were done in tertiary hospitals in the Philippines (Araneta 2001, Aseron-Banaga 2003, Manuel 2005), one was done in Thailand (Chuansumrit 2010), and another in French Guiana (Basurko 2012). Of the retrospective studies, one was done locally (Farol 2003), one was conducted in Thailand (Tantracheewathorn 2007), one was conducted in Brazil (Gibson 2013), and one in India (Gupta 2013).

Four of the nine studies evaluated both clinical and laboratory parameters as risk factors in the development of Dengue Shock Syndrome (Araneta 2001, Tantracheewathorn 2007; Gupta 2011; Manuel 2005). One study evaluated the value of a maculopapular rash in children hospitalized for Dengue (Basurko 2012) and another described clinical warning signs of severe dengue in children during an outbreak (Gibson 2013).

Three studies evaluated laboratory parameters as predictors of severe dengue – 2 of the 3 studies (Aseron-Banaga 2003; Chuansumrit 2010) evaluated laboratory parameters as predictors of severity of Dengue while one study evaluated the correlation between the absolute neutrophil count and morbidity (Farol 2003).

All studies were done in children up to 19 years of age. All of these studies evaluated patients who were hospitalized for Dengue. One of the studies (Araneta 2001)

evaluated patients admitted from the outpatient and admitting section based on pre-defined criteria. None of the studies reviewed directly addressed the question - whether the presence of these clinical signs and symptoms warrant admission, but rather whether these signs and symptoms lead to severe dengue, defined as having dengue shock syndrome.

Table 4. Summary of Studies of Clinical Signs and Symptoms of Dengue Warranting Admission

Study *(Study Design)*	Study Period	Patients (N)	Location	Outcome determined	Remarks
Araneta 2001 *Prospective cohort study*	Aug 1998-Sept 2000	Filipino children 0-12 yrs old with clinical DHF based on WHO criteria (N=62)	Outpatient, admitting section Zamboanga City Med Ctr	Dengue Shock Syndrome	Only patients at one referral center included
Aseron-Banaga 2003 *Prospective cohort study*	Jun-Oct 2002	Filipino children 5mo-18 yrs old with clinical DHF based on PPS 1998 criteria (N=29)	Philippine Children's Medical Center	Severe dengue	Only hospitalized patients recruited
Basurko 2012 *Prospective cohort study*	Nov 2005 – Sept 2006	French Guiana children with dengue-like syndrome, <16 yrs old, (N=110)	French Guiana	Severe Dengue	Only hospitalized patients recruited
Chuansumrit 2010 *Prospective cohort study*	not reported	Thai children, 5-15 yrs old, with clinical DHF based on WHO criteria (N=101)	University Hospital in Thailand	Dengue Shock Syndrome	Only hospitalized patients recruited
Farol 2003 *Retrospective chart review*	June 1997-Sept 2002	Filipino children 4mo-18 yrs old DHF based on PPS 1998 criteria, (N=363)	Private tertiary hospital	Correlation of ANC with DHF morbidity	Only hospitalized patients recruited
Gibson 2013 *Case control study*	Nov 2007-Apr 2008 during an epidemic	Brazilian children < 18 yrs old, (N = 88)	Four tertiary children's hospital in Brazil	Severe dengue	Cases from hospital, controls from community
Gupta 2011 *Retrospective cohort*	2008-2009	Indian children <=18 yrs old with clinical DHF based on WHO criteria, (N = 483)	Hospital in India	Dengue Shock Syndrome	Only records of hospitalized patients reviewed
Tantracheewathorn 2007 *Case control study*	Jan 2003 – Dec 2005	110 DHF and 55 DSS Thai children age < 15 yrs old	Hospital in Thailand	Dengue Shock Syndrome	Simple random sampling of records
Manuel 2005 *Prospective cohort study*	Jan – Sept 2005	Filipino patients 1-19 yrs old clinical DHF based on WHO criteria, (N = 393)	1 public, 1 private hospital in Zamboanga	Dengue Shock Syndrome	Only hospitalized patients recruited

The following clinical and laboratory parameters were evaluated:

- **Shortness of breath –** One study evaluated shortness of breath (Gibson 2013). Presence of this clinical parameter was shown to increase approximately ten times the risk of development of dengue shock OR 9.69 (1.38, 424.74)**,** however, the evidence was graded as **very low** due to risk of bias since patients were not sufficiently homogenous with respect to prognostic factors and the study does not directly answer the question whether this clinical symptom warrants admission, but rather whether these clinical signs and symptoms lead to dengue shock syndrome.
- **Irritablity or drowsiness** - There was one case control study that evaluated irritability and drowsiness on the 4th day and on the 5th day of illness (Gibson 2013). The quality of evidence was graded as very low because the patients were not sufficiently homogenous with respect to the prognostic factors, comparing those with hospitalized severe dengue cases with non-severe dengue in the community and because of indirectness. The study did not directly answer the question whether these clinical signs and symptoms warrant admission, but rather whether these signs and symptoms lead to severe dengue, defined as having dengue shock syndrome. This study showed that irritability or drowsiness was approximately 10 times more likely to be present either on the 4th day of illness (OR 9.9.3, 95% CI 1.47-69.96) or on the 5th day of illness (OR 10.6, 95% CI 1.08-10.84) in those who develop severe dengue. However, the wide confidence intervals may be due to the small sample size.
- **Pleural effusion** - Four studies evaluated pleural effusion using clinical parameters: two were prospective cohort studies (Araneta 2001; Manuel 2005), one retrospective cohort study (Gupta 2011); and one case-control study (Tantracheewathorn 2007). In the case-control study, multivariate analysis did not show pleural effusion to be associated with dengue shock syndrome but the quality of evidence in the case-control one study was graded as **very low** because of imprecision due to the wide confidence intervals that included reduced risk and increased risk of dengue shock (OR 7.9, 95% CI 0.3-243.5; p=0.24). For the three cohort studies, the quality of evidence was graded as **low** because of the possibility of overestimation of treatment effects since the patients were already those hospitalized (Araneta 2001; Manuel 2005; Gupta 2011). Pooled results from these 3 studies showed that the presence of pleural effusion was approximately two times more likely to be present in those with dengue shock, with homogenous results among the studies (OR 2.11, 95% CI 1.30-3.40, p=0.002, I^2=0%).

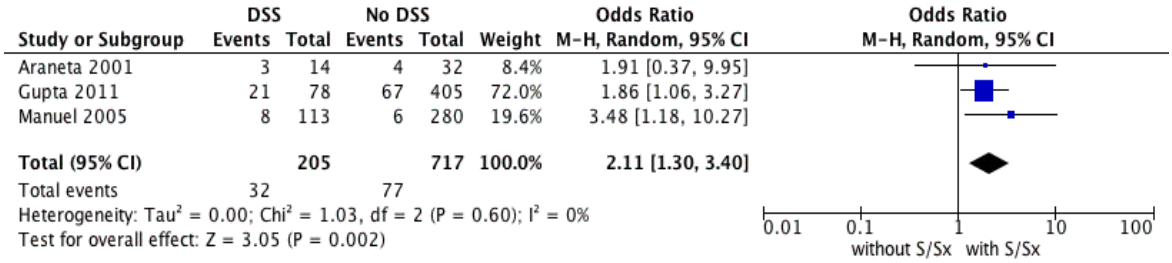

Figure 1. Forest plot of meta-analysis of data for the presence of pleural effusion comparing those with and without DSS in admitted children

- **Abdominal pain:** Three studies evaluated abdominal pain (Gibson 2013; Araneta 2001; Manuel 2005). One case control study (Gibson 2013) evaluated abdominal pain on the 3rd and 4th day of illness. The quality of evidence was graded as **very low** because patients included in the study were not sufficiently homogenous with respect to prognostic factors (groups that were compared were severe vs non-severe dengue) and because of indirectness because the study does not directly answer the question whether this clinical symptom warrants admission, but rather whether this symptom leads to severe dengue. Results showed that abdominal pain was five and seven times more likely to be present on the 3rd day of illness (OR 5.07 95% CI 1.51-18.84) and 4th day of illness (OR 6.92 95%CI 1.38-44.38), respectively, in patients who develop severe dengue. Pooled results for two cohort studies (Araneta 2001, Manuel 2005) also showed that abdominal pain was four times more likely to be present in patients with dengue shock syndrome (OR 3.96 CI 95% 1.24-12.65). The quality of evidence was graded as **low** because of indirectness and because of the risk of bias inherent to the study design and because participants recruited were already the ones hospitalized and thus results may be overestimated. Sample of patients were not representative.

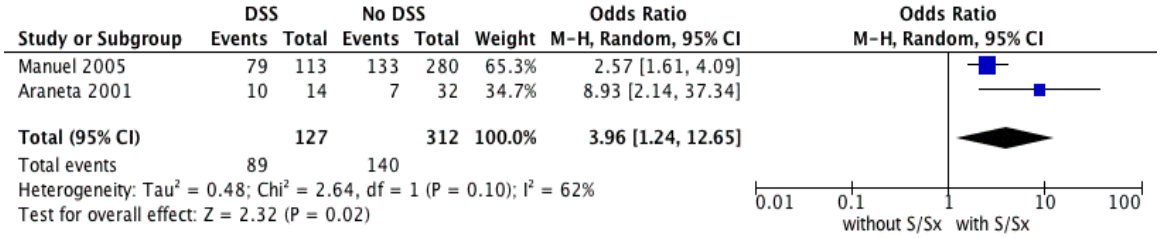

Figure 2. Forest plot of meta-analysis of data for the presence of abdominal pain comparing those with and without DSS in admitted children

- **Bleeding (Melena).** Two cohort studies (Araneta 2001; Manuel 2005) evaluated melena. Results showed that the presence of melena was a risk factor in developing DSS (OR 4.66 CI 95% 1.11-19.51). Quality of evidence was **low** since patients were not homogenous in terms of prognostic factors and those evaluated were those hospitalized.

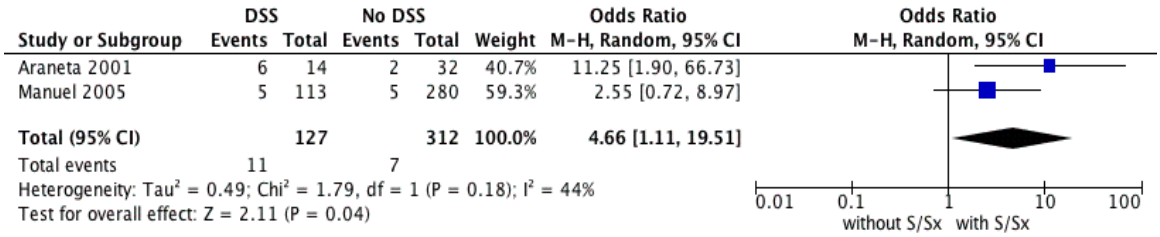

Figure 3. Forest plot of meta-analysis of data for the presence of melena comparing those with and without DSS in admitted children

- **Vomiting:** None of the studies evaluated persistent vomiting. One cohort study (Araneta 2001) showed that vomiting was not a risk factor for the development of dengue shock syndrome (OR 0.63 CI 95% 0.26-1.53). Another study evaluated vomiting (Manuel 2005) but univariate analysis did not show this to be significant and this was not included in the analysis.

The laboratory parameters evaluated were the following:

- **Hemoconcentration ≥ 20% (includes Hct >40%, >50%) -** Five studies evaluated an increased hematocrit as a risk factor but used different cut-off levels to define significant hemoconcentration associated with developing dengue shock syndrome. Two studies (Araneta 2001, Gupta 2011) defined a hematocrit >40% as associated with developing dengue shock syndrome, another study defined hematocrit >50% (Manuel 2005) as significant, a cut-off of hematocrit >42% was used in another (Tantracheewathorn 2007). A fifth study used a rise in hematocrit >25% as significant but also used a combination of rise in Hematocrit >25% and platelet <40,000 as a risk factor for developing dengue shock syndrome. The quality of evidence for two of the studies was **low** because of indirectness and increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors (Chuansumrit 2010, Manuel 2005). The quality of evidence was **very low** in the two pooled studies (Araneta 2001, Gupta 2011) because of indirectness, significant heterogeneity of pooled results, and increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors. The quality of evidence for another study was also **very low** due to indirectness, imprecision, and increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors (Tantracheewathorn 2007). Four of the five studies showed that hemoconcentration was associated with developing dengue shock syndrome. In the studies by Araneta and Gupta, a hematocrit >40 vol. % increased the odds by almost 2 times when pooled (OR 1.65, CI 1.04-2.61). The study by Manuel found hematocrit >50 vol. % to be associated with 5 times risk of developing dengue shock syndrome (OR 4.80, CI 2.26-10.20). In the study by Chuansumrit, a rise in hematocrit >25% was associated with an increased risk of developing dengue shock syndrome by 11 times (RR 11.5, CI 3.3-40.1) while a rise in hematocrit >25% and a platelet count of <40,000 mm^3 increased the risk by 10 times (RR 10.2, CI 3.3-31.2). The study by Tantracheewathorn did not find a hematocrit >42 as a significant risk factor (RR 0.2, CI 0.1-0.5).

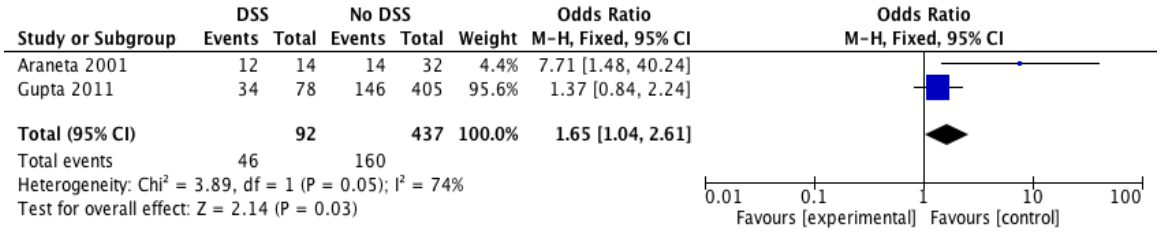

Figure 4. Forest plot of meta-analysis of data for the increased hematocrit (>40vol%) comparing those with and without DSS in admitted children

- **Platelet count < 100,000/mm^3 (*includes <100,000, <50,000, <40,000, < 20,000)*** - Five studies evaluated thrombocytopenia as a risk factor but used different cut-off levels to define significant thrombocytopenia associated with developing dengue shock syndrome. One study associated developing dengue shock syndrome with a platelet count of < 100,000/mm^3, (Araneta 2001), two authors defined significant thrombocytopenia as < 50,000/mm^3 (Manuel 2005;Tantracheewathorn 2007), another study defined a platelet count <40,000/mm^3 as significant (Chuansumrit 2010), while the fifth (Gupta 2011) used a >20,000/mm^3 cut-off. The quality of evidence for four of the studies was **low** because of indirectness in one study (Tantracheewathorn 2007) and because of indirectness and increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors (Araneta 2001, Manuel 2005; Chuansumrit 2010). The quality of evidence was **very low** in one study (Gupta 2011) because of indirectness, imprecision, and increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors. Three of the five studies showed that thrombocytopenia was associated with developing dengue shock syndrome. In the study by Araneta, a platelet count of < 100,000/mm^3 increased the odds by almost 6 times (OR 6.11, CI 1.41-26.41). In the study by Chuansumrit, a platelet count of <40,000/mm^3 increased the risk by 8 times (RR 8.2, CI 1.9-36.7) while the study by Manuel showed that a platelet count < 50,000/mm^3 was associated with almost 2 times odds of developing dengue shock syndrome (OR 1.68, CI 1.08-2.61). The study by Tantracheewathorn did not find thrombocytopenia as a significant risk factor (RR 0.2, CI 0.1-0.5), so did the study by Gupta (OR 1.3, CI 0.59-2.85).

Consideration for recommendation development during Stakeholders Panel meeting:

- There is insufficient evidence to recommend which clinical or laboratory finding could accurately predict development of severe disease and warrant admission.
- The studies evaluated different clinical and laboratory parameters and had different cut-off points for the laboratory parameters tested.
- In the draft recommendation presented to the stakeholders panel, the recommendations for admission to a healthcare facility was platelet count <100,000/mm^3. The Department of Health representatives commented that admitting patients with platelet counts <100,000/mm^3 in an otherwise well child may result in unnecessary hospital admission of those who may be adequately managed on an outpatient basis. There was a consensus among the stakeholders not to put absolute values but use “elevated hematocrit” and “decreased or decreasing platelet count” instead.
- In the absence of published normal values for age of hematocrit among Filipino children, no absolute value for the Hematocrit can be recommended as a cut-off for admission.
- It was also brought up during the stakeholders meeting that there is lack of data for hematocrit values for patients with iron deficiency anemia or hematologic disorders who subsequently develop dengue.

- It was emphasized that the criteria for admission should take into consideration the overall clinical condition of the child rather than focusing on platelet count or hematocrit values alone.
- Representatives of the PNSP emphasized that urine output should be one of the parameters to be evaluated in considering admission**.** However, there were no studies that evaluated this outcome

Question 2: Among patients with dengue, which risk factors are associated with mortality?

Recommendation 1:
Patients with dengue who present with any one of the following clinical findings may be at increased risk for mortality.

- Hypotension on admission
- Narrow pulse pressure on admission
- DHF stage 3 and 4 (severe dengue)
- History of previous dengue
- Prolonged shock
- Respiratory failure
- Liver failure (AST elevation > 200 u and INR > 1.3)
- Renal failure (BUN >20 mg% and serum Creatinine >1.0mg %)
- Significant bleeding including gastrointestinal bleeding
- Severe plasma leakage in multiple sites (pleural effusion, pericardial effusion and ascites)

(Strong recommendation, based on moderate, low and very low quality evidence)

Recommendation 2: The presence of two or more of the following warning signs in patients with dengue may increase the risk for mortality:

- severe abdominal pain
- arterial hypotension
- neurologic manifestation
- painful hepatomegaly
- hypovolemic shock
- liver failure
- myocarditis

(Strong recommendation, based on very low quality evidence)

Recommendation 3 : Patients with dengue who present with one or more of the following laboratory findings may be at increased risk for mortality and warrant hospital admission for close monitoring:

- Decline in Hgb by ≥20%
- Thrombocytopenia, with APC ≤ 50,000
- Hemoconcentration, with Hct > 40 % or 20% increase in lowest and highest hematocrit
- Creatinine > 1 mg %
- AST > 1000 u
- Acidosis

(Strong recommendation, based on moderate, low and very low quality evidence

Recommendation 4: Prothrombin time (PT) and Partial Prothrombin Time (PTT) do not differentiate those who may be at increased risk for mortality and are not recommended as routine tests for patients with dengue**.**

(Strong recommendation, based on low quality evidence)

Summary of Evidence

Six studies evaluated demographic, clinical and laboratory findings that may serve as risk factors for mortality in patients with dengue: two were prospective cohort studies (Abiera 1996, Chua 1993), two more were retrospective cohort studies (Bunnag 2011, Fajardo 1996), one was a case control study (Moraes 2013), and another one was a cross sectional study (Mena Lora 2014). Of the six studies, five looked at both clinical and laboratory parameters (Abiera 1996, Bunnag 2011, Moraes 2013, Mena Lora 2014, and Fajardo 1996) while the study by Chua, 1993 looked at laboratory parameters only. Moraes, 2013 was the only study that included demographic risk factors. Various clinical parameters were evaluated and differed in the six studies.

The two prospective cohort studies were conducted locally among pediatric patients admitted with a diagnosis of DHF/DSS in the same university tertiary hospital. The study by Abiera 1996 included 66 patients who fulfilled the criteria for DHF/DSS set by WHO (1986) and were serologically confirmed for dengue virus by IgM ELISA technique. This study determined clinical manifestations and hematologic parameters as possible risk factors for mortality and bleeding. Abiera 1996 reported relative risks for each factor and relative risks for combinations of these factors among those patients with prolonged PTT. The second prospective cohort study was by Chua 1993 which was conducted on 89 patients aged <18 years old who fulfilled the WHO criteria for DHF. Only hematologic parameters: platelet count, prothrombin time and PTT were evaluated for association with mortality in this study.

The quality of evidence of both prospective cohort studies was **low**. There was a serious risk of bias as participants were recruited from a tertiary hospital and there was not enough information on whether participants or subgroups of participants were sufficiently homogenous with respect to prognostic factors.

There were two retrospective cohort studies, one done in a tertiary pediatric hospital in the Philippines (Fajardo 1996) and another in a tertiary hospital in Bangkok, Thailand (Bunnag 2011). The local study looked at 201 cases of DHF/DSS admitted from 1981 to 1991 who satisfied the WHO-DOH criteria. The study by Bunnag 2011 limited their review to 50 Dengue pediatric patients who presented with shock at the ER. DSS was classified using the 1997 WHO criteria, and were serologically and virologically confirmed dengue cases. These studies evaluated the association of both clinical presentation and hematologic parameters with mortality.

The quality of evidence from Fajardo 1996 was graded as **moderate** because of serious risk of bias since the study was conducted in a tertiary hospital. The quality of evidence of the study by Bunnag 2011 is **low** because the study focused on DSS patients (i.e. more severe cases) from a tertiary referral hospital in Thailand. Both studies had an increased risk for bias due to lack of information if subjects were sufficiently homogenous with respect to prognostic factors.

The case control study (Moraes 2013) was a population-based study from Brazil which used the country's National Notifiable Diseases Surveillance System (SINAN). It included 12,321 severe dengue cases from all age groups who were registered in SINAN. Case confirmation was made using clinical, epidemiologic, or laboratory criteria,

with > 50% of severe dengue cases confirmed through laboratory measures. Factors examined were demographic, clinical manifestations and hematologic parameters.

The quality of evidence from this study was graded as **very low** due to a serious risk of bias since the study population was limited to cases of severe dengue, insufficiency of information on whether participants were homogeneous with respect to risk factors and because of indirectness since both adults and children were enrolled in the study.

The last study was a cross sectional study (Mena Lora 2014) conducted in a referral general pediatric hospital in the Dominican Republic. Records of 796 children, clinically diagnosed using the 2009 WHO case definition for dengue, were reviewed for clinical and hematologic risk factors. This study had **low** quality of evidence. Only admitted patients in a tertiary pediatric referral hospital were included, that may be a cause for a serious risk for bias. There was also lack of information on whether participants were homogeneous with respect to prognostic factors.

Table 5. Summary of Studies on Risk Factors for Mortality in Dengue

Study *(Study Design)*	Study Period	Patients (N)	Location	Outcome determined	Remarks
Abiera 1996 *Prospective cohort*	Jan-Dec 1993	Filipino children 4 mos-17 yrs old with clinical DHF/DSS based on WHO criteria (N=66)	Tertiary private university hospital in Manila	Clinical manifest-ations and laboratory parameters associated with mortality	Serologically confirmed by IgM ELISA
Bunnag 2011 *Retrospecti ve cohort*	Jan 2008-Dec 2009	Thai children < 1yo->15 yrs old with DSS based on WHO criteria 1997 (N=50)	Tertiary hospital in Bangkok	Clinical manifestations and laboratory parameters associated with mortality	All serologically and/or virologically confirmed
Moraes 2013 *Case control*	Jan 2000-Dec 2005	All age groups in Brazil with severe dengue registered in National Notifiable Disease Surveillance System (SINAN) in Brazil (N=12,321)	National Notifiable Disease Surveillance System (SINAN) in Brazil	Clinical, demographic and laboratory parameters associated with mortality	
Mena Lora 2014 *Cross sectional study*	2011-2012	1-16 yrs old from Dominican Republic with Dengue based on 2009 WHO case definition on severity (N=796)	Children's hospital in Dominican Republic	Clinical manifestations and laboratory parameters associated with mortality	
Chua 1993 *Prospective cohort*	June-Dec1992	Filipino children 6 mos-18 yrs old with DHF based on 1997 WHO criteria (N=89)	Tertiary private university hospital in Manila	Laboratory parameters associated with mortality	
Fajardo 1995 *Retrospecti ve cohort*	Jan 1981-Dec 1991	Filipino children 6 mos-240 mos with DHF/DSS based on 1997 WHO criteria (N=201)	Tertiary children's hospital in Manila	Clinical manifestations and laboratory parameters associated with mortality	

The clinical parameters that were evaluated were the following:

Clinical Parameters

- **Hypotension on Admission:** There was one study that evaluated this parameter (Fajardo 1996). No definition of hypotension was provided in the study. Cases who presented with hypotension on admission was highly associated with mortality (OR 18.27; 95% CI 6.72, 49.88). [Quality of evidence was **moderate**]
- **Narrow Pulse Pressure:** There was one study with **moderate** quality of evidence that evaluated this parameter (Fajardo 1996). Cases who presented with narrowed pulse pressure on admission were 3 times more likely to die (OR 3.82, 95% CI 1.65, 8.88).
- **DHF 3 and 4:** There was one study with **moderate** quality of evidence that evaluated this parameter (Fajardo 1996). Cases with DHF grades III and IV had an increased risk for mortality (OR 7.58, 95% CI 2.5-23.0).
- **Previous Dengue:** Only one study evaluated this parameter (Fajardo 1996). There was a significantly increased risk for mortality among those with previous history of dengue (OR 4.7, 95% CI 1.77-12.72). The quality of evidence was **moderate**.
- **Prolonged Shock:** There was one study that evaluated this parameter (Bunnag 2011). This study focused on dengue patients who presented with shock at the ER. Prolonged shock was not defined. It was strongly associated with mortality however, it had **low** quality of evidence due to the wide confidence interval (OR=191.4; 95% CI 8.09, 4526.44) probably due to the small number of subjects with prolonged shock in the studied population.
- **Liver Failure:** There was one study that evaluated this parameter (Bunnag 2011). This study focused on dengue patients who presented with shock at the ER. Liver failure was defined as AST elevation > 200 u and INR > 1.3 while hepatic encephalopathy was not defined. The presence of liver failure was a significant factor strongly increasing the risk for mortality however the **low** quality evidence was due to the wide interval estimates (OR 37.19; 95% CI 1.9, 729.18). In contrast, hepatic encephalopathy had no effect (OR 2.0; 95%CI 0.19, 21.62).
- **Respiratory Failure:** There was one study with **low** quality of evidence that evaluated this parameter (Bunnag 2011). This study focused on dengue patients with shock at the ER. Presence of respiratory failure strongly increases the risk for mortality (OR 66; 95%CI 4.57, 953.28).
- **Renal Failure:** One study with **low** quality of evidence evaluated this parameter (Bunnag 2011). This study focused on dengue patients with shock at the ER. Renal failure was defined in the study as elevation of BUN>20 mg% and serum Creatinine > 1.0mg %. The presence of renal failure was strongly associated with death (OR 176; 95%CI 9.17, 3378.87). The wide confidence interval could be due to the small number of subjects with renal failure among the studied population.
- **Bleeding:** There were three studies that evaluated this parameter (Abiera 1996, Bunnag 2011, Moraes 2013). Any bleeding was not seen to be associated with mortality risk (OR 0.41; 95%CI 0.41, 141.31). However in the two other studies, GI bleeding and significant bleeding increased the risk for death (OR 2.10 and OR 19.67, respectively). These latter two studies were done on patients with severe dengue which may produce bias. Definition of significant bleeding was not described by Bunnag 2011. The quality of evidence was **low** for two studies (Abiera 1996: Bunnag 2011) and **very low** in one study **(**Moraes 2013)
- **Effusion:** There were two studies that evaluated this parameter (Abiera 1996, Moraes 2013). Abiera 1996 performed ultranosographic examination of the lungs to

confirm clinical evidence of pleural effusion. Moraes on the other hand, included different cavitary effusions: ascites, pleural effusion and pericardial effusion in his analysis. Pleural effusion alone as reported by Abiera was not significantly associated with mortality (OR 0.11; 95% CI 0.01, 1.99; **low** quality evidence), but presence of cavitary effusions increased the risk for dying 2-fold in the study by Moraes 2013 (OR 2.11; 95% CI 1.51, 2.96; **very low** quality of evidence)

- **Warning Signs *Severe abdominal pain, arterial hypotension, neurologic manifestation, painful hepatomegaly, hypovolemic shock, hepatic failure and myocarditis.** There was one study that evaluated this parameter (Moraes 2013), however with **very low** quality of evidence. A strong positive gradient for the risk of dying from severe dengue was found with increasing number of warning signs starting from 2 (OR 1.99; 95% CI 1.56, 2.54) to ≥ 4 warning signs (OR 11.98; 95% CI 7.60, 18.91). The study, however, did not include a definition for each of these warning signs.
- **Vomiting:** Only one study that evaluated this parameter (Mena Lora 2014). Presence of vomiting increased the risk for death almost 10 times (OR 9.8; 95%CI 2.9, 33.3). The quality of evidence was **low**.

Laboratory Parameters

- **Decline in Hemoglobin:** There was one **moderate** quality study that evaluated this parameter (Fajardo 1996). With ≥20% drop of hemoglobin, the risk for mortality increased 4-5 times (OR 4.59, 95% CI 1.92, 10.98).
- **Increased Hematocrit:** There were two studies that evaluated this parameter (Fajardo 1996, Moraes 2013). One study had **moderate** quality evidence (Fajardo 1996) and the other had **very low** quality evidence (Moraes 2013). Definitions for increase in hematocrit were overlapping: Fajardo defined it as >40% Hct rise while in Moraes, it was an increase ≥45% for ≤14 years old OR 20% difference between highest and lowest Hct determinations. Both studies were consistent in showing an association in risk for mortality. (Fajardo: OR=4.83; 95 CI 1.92, 12.11 and Moraes: Adj OR=2.47; CI 1.86, 3.29).
- **Thrombocytopenia:** There were three studies that evaluated this parameter (Mena Lora 2014, Chua 1993, Fajardo 1996). Two studies had **low** quality of evidence (Mena Lora 2014; Chua 1993) and one study had **moderate** quality of evidence (Fajardo 1996). Different platelet levels were analyzed for risk of mortality in the studies but were consistent in reporting an increase in risk for mortality. Mena Lora 2014 showed that actual platelet count (APC) <30,000 had a three-fold increase in risk (OR 2.9; 95%CI 1.4, 5.9), while APC <50,000-20,000 resulted in 6 times increases in risk (Chua 1993: OR 6.08; 95%CI 1.17, 31.66). This increased risk was likewise seen the study by Fajardo 1996 with APC ≤50,000 on admission (OR 9.32; 95%CI 3.43, 25.29) and those with nadir of APC <50,000 during the hospital stay (OR 6.95; 95%CI 2.86, 16.92).
- **Creatinine Levels:** One **low** quality study evaluated this parameter (Bunnag 2011). This study focused on dengue patients with shock at the ER. Patients with creatinine level rose to > 1 mg% had a significantly increased risk for mortality (OR 120; 95%CI 6.21, 2319.69). Again, the interval estimate was noted to be very wide.
- **AST levels:** There was one study with **low** quality evidence that evaluated this parameter (Bunnag 2011). This study focused on dengue patients with shock at the ER. Cases with AST > 1000 u had an increased risk for mortality (OR 18; 95%CI 1.77, 183.42) with a wide interval estimate.

- **Acidosis:** There was one study with **low** quality evidence that evaluated this parameter (Bunnag 2011). This study focused on dengue patients with shock at the ER. Cases with acidosis have an increased risk for mortality (OR 15.38; 95%CI 1.95, 120.98) with a wide interval estimate.
- **Prolonged Partial Thromboplastin Time (PTT):** There were three studies that evaluated this parameter (Abiera 1996, Bunnag 2011, Chua 1993), and all had **low** quality of evidence. Results were not consistent and inconclusive. Bunnag reported that although prolonged PTT increased the risk for mortality, this was not significant (OR 14.57 95%CI 0.76, 280.39). On the other hand, Chua 1993 showed that longer prolonged PTT had increased mortality risk (PTT 11-20 sec: 5% risk, PTT 21-30 sec: 25% risk, PTT >30sec: 40% risk) and in Abiera 1996, PTT >20 sec was strongly associated with OR = 16.47 (95% CI could not be estimated).
- **Prolonged Prothrombin Time (PT):** There was one study **low** quality of evidence that evaluated this parameter (Chua 1993). There was an increased risk for mortality with prolonged PT but this was not positively correlated with degree of prolongation (PT prolonged 1-10 sec: 18% risk, PT prolonged 11-20 sec: 25% risk, PT $\geq$21 sec: 17% risk).
- **Albumin Levels:** There was one study with **low** quality evidence that evaluated this parameter (Bunnag 2011). This study focused on dengue patients with shock at the ER. The mean albumin levels among those who died were significantly lower than those who survived, with a median level of 1.06 g% (95 CI 0.48, 1.64).

Consideration for recommendation development during Stakeholders Panel meeting:

- There is insufficient evidence to recommend which clinical or laboratory finding could accurately determine mortality.
- Many findings were based on single studies or from studies that were inconsistent that could be a result of differences in study design and patient populations.
- In one study, vomiting was shown to increase risk of mortality (Mena Lora 2014). This was noted to be in conflict with the recommendation in CPG Question 1 stating that vomiting was not associated with increased risk for development of dengue shock syndrome. The Stakeholders panel voted to remove this recommendation since it was based on a single study with low quality evidence.

Question 3: Among patients admitted because of dengue, which clinical signs and/or laboratory findings indicate significant bleeding?

Recommendation 1:
Among patients admitted because of dengue, the presence of one or more of the following clinical or laboratory findings may increase the risk of bleeding

- Hypotension
- Narrow pulse pressure
- Hepatomegaly
- Platelet count < 50,000/mm3
- WBC count < 5000/mm3
- Elevated ALT (> 3x the normal value)

(Strong recommendation, based on low to very low quality evidence)

Recommendation 2:
Among patients admitted because of dengue, there is some evidence to suggest that the following signs and symptoms may be associated with significant bleeding.

- Vomiting
- Abdominal pain
- Restlessness
- Pleural effusion or ascites
- Rash

(Strong recommendation, based on low to very low quality evidence)

Recommendation 3:
Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) were not shown to be significantly associated with bleeding and should not be routinely done in patients with dengue.
(Strong recommendation, based on very low quality evidence)

Summary of Evidence

Four studies evaluated both clinical features and laboratory findings that may serve as predictors for bleeding in patients with dengue: three studies were prospective cohort studies (Carlos 2005; Abiera 1996; Diaz-Quijano 2010) one study was a case control study (Shivbalan 2004). One retrospective cross sectional study evaluated only clinical parameters that could be used to predict bleeding (Abad 1998 unpublished). An additional two studies, one a prospective cohort study (Chua 1993) and the other a retrospective cross-sectional study (Rubio 2007) determined only laboratory parameters that may predict development of spontaneous bleeding in patients with dengue. Various clinical parameters were evaluated and differed in the studies.

Of the three prospective studies, two were conducted in patients admitted in different tertiary hospitals in the Philippines (Carlos 2005; Abiera 1996) and one was conducted among outpatients in Colombia (Diaz-Quijano 2010). One local study was undertaken to determine differences in clinical features and hematologic abnormalities between patients with DF and DHF who were hospitalized in a tertiary medical center in Quezon City Philippines (Carlos 2005). Of the 359 dengue patients aged 2 to 17 years old confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) and/or IgM ELISA and included in the study, 239 were diagnosed as DF and 120 with DHF based on WHO criteria (WHO 1997). The second prospective cohort study enrolled pediatric

patients aged 4 months to 17 years old admitted in a university tertiary hospital in Manila (Abiera 1996). This study determined clinical and hematologic parameters that would predict mortality and bleeding in 110 patients with DHF or DSS. The third prospective cohort study was conducted in 4 municipalities in a hyperendemic area in northeastern Colombia (Diaz-Quijano 2010). The study enrolled 750 patients, both children and adults aged at least 5 years old (age range 5-85 years) with laboratory confirmed dengue (based on viral isolation or serology) who were followed up to determine clinical manifestations and laboratory tests that can predict spontaneous bleeding. Outcome was defined as any spontaneous non-cutaneous bleeding, i.e. epistaxis, hematemesis, melena, urinary or genital hemorrhage.

The case control study was conducted in a tertiary medical center in Chennai, India and enrolled 132 infants and children diagnosed to have dengue infection based on clinical criteria and/or positive dengue IgG or IgM (Shivbalan 2004). Various clinical and laboratory parameters present during hospitalization were analyzed to assess their value as predictors for spontaneous cutaneous and mucosal bleeding in dengue infection.

One retrospective study enrolled pediatric patients below 15 years old who were all diagnosed to have DHF based on WHO criteria (WHO 1997) (Abad 1998 unpublished). The study was conducted in a university tertiary hospital in the Philippines. Of the 145 patients studied, 46 had no bleeding while 99 developed bleeding after admission and during hospital stay. Pre-determined clinical manifestations that may predict bleeding were compared in the two groups.

There were two studies that evaluated selected hematologic parameters as predictors of bleeding. Both studies were conducted in the Philippines, although one trial enrolled only pediatric patients aged 6 months to 18 years old (Chua 1993) and the other one enrolled both adolescents and adults aged at least 14 years old (Rubio 2007). In both studies, the diagnosis of dengue was based on the clinical parameters set by the WHO (WHO 1997) and no laboratory confirmation was performed. The study by Chua 1993 included 89 pediatric patients admitted in a tertiary university hospital in Manila with a diagnosis of DHF or DSS. In this study, the association of reduced platelet count with mortality was determined in 89 patients and the association of prolongation of the platelet count and partial thromboplastin time with bleeding was evaluated in 59 patients. The second study was conducted in a tertiary hospital in northern Philippines and enrolled 215 adolescents and adults, of whom 20 had bleeding episodes during the course of the illness.

Table 6. Summary of Studies on Clinical Signs and/or Laboratory Findings Indicating Significant Bleeding in Dengue Patients

Study *(Study Design)*	Study Period	Patients (N)	Location	Outcome determined	Remarks
Abad 1998 *Retrospective study*	Jan 1994 - Sep 1998	Filipino children 0-15 yrs old with clinical DHF based on WHO criteria (N=145)	Tertiary private university hospital in Manila	Clinical manifestations and demographic factors associated with bleeding	No laboratory confirmation of dengue diagnosis
Abiera 1996 *Prospective cohort*	Jan 1993 - Dec 1993	Filipino children <18 yrs old with clinical DHF/DSS confirmed by dengue IgM antibody test (N=66)	Tertiary private university hospital in Manila	Clinical presentation, demographic factors and laboratory findings associated with mortality (primary outcome) and significant bleeding (secondary outcome)	Small sample size
Carlos 2005 *Prospective cohort*	Jan 1999 -Dec 2001	Filipino children 2-17 yrs old with clinical dengue confirmed by dengue PCR and/or dengue IgM antibody test (N=359)	Tertiary private hospital in Quezon City	Clinical manifestations and hematologic abnormalities differentiating DF from DHF	Indirectness due to differences in outcome evaluated
Chua 1993 *Prospective cohort*	Jun 1992 – Dec 1992	Filipino children 0-15 yrs old with clinical DHF/DSS based on WHO criteria (N=89)	Tertiary private university hospital in Manila	Hematologic parameters (Hct, plt count, PT, PTT) associated with mortality; association of PT and PTT with bleeding	Only 59 out of 89 were included in the analysis of bleeding
Rubio 2007 *Retrospective cross sectional study*	Jan 2006 – Dec 2006	Filipino patients >14 yrs old with DF/DHF based on National Guidelines for Clinical Mx of Dengue Syndrome (N=215)	Tertiary hospital in Davao	Leukocyte count, plt count associated with incidence of bleeding	No laboratory confirmation of dengue diagnosis; Indirectness since only adults and adolescents were studied
Diaz-Quijano 2010 *Prospective cohort*	Not reported	Colombian children and adults 5-85 yrs old with dengue based on WHO criteria and confirmed by viral culture or serology (N=729)	4 municipa-lities in a hyperendemic area in northeastern Colombia (outpatient)	Clinical manifestations and hematologic factors associated with noncutaneous bleeding	Included both adults and children
Shivbalan 2004 *Case control study*	Aug 2001 – Feb 2002	Indian children diagnosed with DF/DHF/DSS based on WHO criteria (N=104)	Tertiary private university hospital in India	Clinical manifestations and laboratory findings associated with bleeding	Only 93 out of 104 (89%) were positive for dengue IgM, IgG or both; Laboratory tests were inconsistently performed

The clinical parameters that were evaluated were the following:

- **Hypotension:** There was one study that evaluated hypotension as a clinical predictor for bleeding (Abad 1998). The quality of evidence was **very low** because there was insufficient information on how patients were recruited and whether they were a representative sample or were homogenous with respect to prognostic factors and imprecision. This study showed that hypotension significantly increased the risk for bleeding in dengue patients, (OR 35.28, 95% CI 2.1-592.46). The wide confidence interval could be due to the small number of subjects with bleeding.
- **Narrow pulse pressure:** There were two studies that evaluated this outcome (Abad 1998; Shivbalan 2004). The quality of evidence was graded as **low** in one study because of increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors (Shivbalan 2004) and **very low** in the other study because there was insufficient information on how patients were recruited and whether they were a representative sample or were homogenous with respect to prognostic factors (Abad 1998). Both studies showed that narrow pulse pressure may be associated with spontaneous bleeding in patients with dengue, however in one study (Abad 1998) the results showed wide confidence intervals (OR 42.77, 95% CI 2.55-716.4) while the other study (Shivbalan 2004) was significant only in univariate analysis (OR 4.00, 95% CI 1.61-9.93) but was not shown to be statistically significant in the logistic regression analysis.
- **Hepatomegaly/hepatosplenomegaly:** There were two studies that evaluated this outcome (Abad 1998; Abiera 1996). The quality of evidence was graded as **low** in one study because of increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors (Abiera 1996) and **very low** in the other study because there was insufficient information on how patients were recruited and whether they were a representative sample or were homogenous with respect to prognostic factors (Abad 1998). The two studies showed contradictory results because one study (Abiera 1996) showed that hepatomegaly increased the risk of bleeding by approximately 6 times (OR 6.62, 95% CI 2.15 – 20.42) but in another study (Abad 1998) hepatosplenomegaly was not shown to predict those who would bleed compared to those who would not (OR 3.96, 95% CI 0.48-32.61). Another study evaluated liver tenderness as a clinical predictor for spontaneous bleeding (Shivbalan 2004) and reported that liver tenderness was associated with bleeding only on univariate analysis (OR 3.24, 95% CI 1.47-7.14) but the results were not significant on logistic regression analysis.
- **Vomiting**: There were two studies that evaluated the risk for bleeding in those with vomiting (Abad 1998; Diaz-Quijano 2010). The quality of evidence for two studies was graded as **low** because of indirectness since both children and adults were enrolled (Diaz-Quijano 2010) and one was graded as **very low** because there was insufficient information on how patients were recruited and whether they were a representative sample or were homogenous with respect to prognostic factors (Abad 1998). The two studies showed contradictory results since one study (Diaz-Quijano 2010) showed that vomiting increased the risk for spontaneous bleeding (OR 1.46, 95% CI 1.19-2.96) while the other study did not (OR 1.31, 95% CI 0.65-2.64; Abad 1998).
- **Abdominal pain**: There were four studies that evaluated this clinical parameter (Carlos 2005; Shivbalan 2004; Diaz-Quijano 2010; Abad 1998) The quality of evidence was graded as **low** in two studies because of increased risk of bias due to insufficient information on whether participants were representative or sufficiently

homogenous with respect to prognostic factors in two studies (Shivbalan 2004) and because of indirectness since both adults and children were enrolled in one study (Diaz- Quijano 2010). Two studies were graded to have **very low** quality of evidence because there was insufficient information on how patients were recruited and whether they were a representative sample or were homogenous with respect to prognostic factors (Abad 1998; Carlos 2005). In addition, there was no laboratory confirmation of dengue in one study (Abad 1998) and one did not directly determine development of bleeding but rather compared those who developed DHF with those who developed DF (Carlos 2005). The studies showed contradictory results. Carlos et al showed that significantly more patients were diagnosed to have DHF compared to DF when abdominal pain was present before admission (OR 1.83; 95% CI 1.17-2.88) or at the time of admission (OR 1.83; 95% CI 1.15-2.89). The study of Abad 1998 showed that abdominal pain increased the risk of bleeding by almost 4 times (OR 3.94, 95% CI 1.76-8.80). However, the study by Diaz-Quijano showed that abdominal pain was shown to decrease the risk of bleeding (OR 0.39 (95% CI 0.24-0.64) while the study by Shivbalan showed that the presence of abdominal pain at anytime during the course of the disease was not found to increase nor decrease the risk of bleeding (OR 2.401, 95% CI 0.928-6.208).

- **Restlessness**: There were no studies that evaluated restlessness with development of bleeding. One study compared the presence of restlessness on admission in those with DF and DHF (Carlos 2005). The quality of evidence was graded as **very low** because of increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors, indirectness of the outcome evaluated, and wide confidence intervals around the measured effect. This study showed that the presence of restlessness did not significantly differentiate those with DF from those with DHF (OR 18.58, 95% CI 0.99-348.12).
- **Serosal effusion (pleural effusion or ascites)**: Three studies evaluated this clinical parameter: the presence of pleural effusion was evaluated by chest-xray in one study (Shivbalan 2004), by chest ultrasound in another study (Abiera 1996), and the third study did not specify the method used for evaluating the presence of pleural effusion or ascites (Abad 1998). The quality of evidence for two studies was graded as **low** because of increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors (Abiera 1996; Shivbalan 2004) and one was graded as **very low** because there was insufficient information on how patients were recruited and whether they were a representative sample or were homogenous with respect to prognostic factors (Abad 1998). In two studies, the presence of pleural effusion alone or both pleural effusion and ascites were found to increase the risk for bleeding (Abiera 1996; Abad 1998). The studies showed that the presence of pleural effusion or ascites was found to increase the risk for bleeding by approximately 4 times more compared to those with no effusion. In the study of Abiera, computed OR was 3.85 (95% CI 1.31-11.32) and in the study by Abad, the computed OR was 3.86 (95% 1.09-13.68; p=0.04). In the third study (Shivbalan 2004), the presence of pleural effusion was found to be significantly associated with spontaneous bleeding by univariate analysis (OR 2.49, 95% CI 1.07-5.78) but this was not found to be significant by logistic regression.
- **Rash**: There was one study that evaluated rash as a clinical predictor for bleeding in patients with dengue (Diaz-Quijano 2010). The quality of evidence was graded as **low** because of indirectness since both children and adults were enrolled. Results showed that the presence of rash was significantly associated with bleeding (OR 1.66, 95% CI 1.25-2.2). However, the type of rash (e.g. petechial) was not described.

The presence of the following laboratory parameters and the risk for bleeding in dengue patients were evaluated:

- **Thrombocytopenia:** Three studies evaluated the presence of thrombocytopenia with bleeding but used various cut-off levels to define significant thrombocytopenia. One study (Rubio 2007) determined the association of bleeding with the mean platelet counts, subdivided into different levels of thrombocytopenia (mild 100,000 to <150,000/mm^3; moderate 50,000 to <100,000/mm^3; severe 20,000 to <50,000/mm^3; very severe <20,000/mm^3). Another study defined significant thrombocytopenia as platelet count < 90,000/µL (Diaz-Quijano 2010) and the other study defined significant thrombocytopenia as platelet count <50,000/mm^3 (Shivbalan 2004). The quality of evidence for two studies was **low** because of indirectness in one study (Diaz-Quijano 2010) and because of increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors (Shivbalan 2004). The quality of evidence was **very low** in one study because of insufficient information on how patients were recruited and whether they were a representative sample or were homogenous with respect to prognostic factors and also because of indirectness since only adolescents and adults were enrolled (Rubio 2007). All three studies showed that thrombocytopenia was associated with increased risk for bleeding. In the study by Diaz-Quijano, a platelet count below 90,000/µL increased the odds of bleeding by almost 2 times compared to those with no bleeding (OR 1.8, 95% CI 1.1-2.94). In another study, bleeding was approximately 4 times more likely in those with a platelet count <50,000/mm^3 (Shivbalan2004). In the study by Rubio, bleeding was significantly associated with a platelet count below <50,000/mm^3 (OR 77.65, 95% CI 4.56-1235.50). The wide confidence interval could be due to the small number of events (20 patients with spontaneous bleeding).
- **Leukopenia:** The two studies that evaluated this outcome used different cut-off points for determining leukopenia. Both studies defined leukopenia as white blood cell (WBC) count of <5000/mm^3 (Rubio 2007) while the other study used a WBC count <4500/µL to define leukopenia (Diaz-Quijano 2010). The quality of evidence was **very low** in the study by Rubio 2007 because of insufficient information on how patients were recruited and whether they were a representative sample or were homogenous with respect to prognostic factors and also because of indirectness since only adolescents and adults were enrolled). The quality of evidence for the other study was **low** because of indirectness (Diaz-Quijano 2010). Both studies showed that leukopenia was associated with an increased risk of bleeding. In the study by Rubio, a WBC count of < 4500/mm3 increased the odds of bleeding by almost 2 times (OR 1.87, 95% CI 1.19-2.96; p=0.007) whereas the study by Diaz-Quijano 2010 showed an increase in bleeding by approximately 5 times (OR 5.23, 95% CI 1.1.8-23.13).
- **Elevated serum alanine aminotransferase (ALT):** One study determined the association of elevated ALT with spontaneous bleeding in dengue patients (Shivbalan 2004). The quality of evidence was graded as **low** because of increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors. ALT elevated more than 3 times the normal value increased the odds of bleeding by almost 3 times (adjusted OR 2.95, 95% CI 1.21-6.67).
- **Prolonged Prothrombin (PT) Time:** Only one study evaluated the risk of bleeding with prolonged PT (Chua 1993). The quality of evidence for this study was graded as **very low** because of serious risk of bias due to inadequate information on patient recruitment, selective performance of PT (PT was not performed on all patients), and

imprecision. This study showed that there was no significant difference in PT among those with bleeding compared to those without bleeding (OR 2.70, 95% CI 0.71-10.23).

- **Prolonged Partial Thromboplastin Time (PTT):** There were three studies that evaluated this outcome (Abiera 1996; Chua 1993; Shivbalan 2004). The quality of evidence for two studies was graded as **low** because of increased risk of bias due to insufficient information on whether participants were representative or sufficiently homogenous with respect to prognostic factors (Abiera 1996; Shivbalan 2004). The other study was graded as **very low** because of serious risk of bias due to inadequate information on patient recruitment, PT was not performed on all patients, and imprecision (Chua 1993). In Shivbalan 2004, PTT was not found to be significantly associated with spontaneous bleeding by logistic regression analysis although prolonged PTT was not defined. One study (Chua 1993) did not show a greater tendency to bleed in those with PTT prolonged by >30 second (OR 1.71, 95% CI 0.28-10.49). Another study showed that regardless of degree of prolongation of PTT (>10 seconds, >20 seconds, > 30 seconds, > 40 seconds), PTT was not correlated with the risk for bleeding (Abiera 1996).

Consideration for recommendation development during Stakeholders Panel meeting:

- There is insufficient evidence to recommend which clinical or laboratory finding could accurately determine development of spontaneous bleeding.
- Although There is some evidence that ALT>3x normal value may increase the risk of bleeding, the DOH representatives mentioned that not all facilities in the field can test for ALT
- There was one study that showed that rash was significantly associated with bleeding, however it was not mentioned whether the rash was petechial or not. Although the initial recommendation specified petechial rash as a possible risk factor, the stakeholders decided that unspecified rash be used to avoid misquoting the study.

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CHAPTER 3

FLUID THERAPY FOR DENGUE

Maintenance intravenous fluids are commonly used in hospitalized children for maintaining fluid and electrolyte balance and homeostasis. Hypotonic fluids are the most commonly used type of fluids for children admitted in a hospital. Sick children are in a stressed state and secrete antidiuretic hormone (ADH) more than healthy children. This increased ADH secretion leads to water retention by the kidneys which in turn leads to hyponatremia defined as plasma sodium content (pNa < 136 mol/L). Early symptoms of hyponatremia include headache, nausea, and general malaise, progressing to seizures and coma, or even death without appropriate management (Easley 2013).

In the WHO 2009 guidelines, ambulatory patients are encouraged oral intake of oral rehydration solution, fruit juice and other fluids containing electrolytes and sugar to replace losses from fever and vomiting. Adequate oral fluid intake may reduce the number of hospitalizations. However, fluids containing high sugar or glucose should be avoided because they can exacerbate hyperglycemia of physiological stress from dengue (WHO 2009).

An ideal physiologic fluid is one that resembles the extracellular and intracellular fluids closely (WHO 2009). If the patient develops warning signs but without shock, the recommendation is to give isotonic solutions such as 0.9% Saline or Ringer's Lactate. Frequent re-assessment of the clinical status and hematocrit should be done and fluid infusion rates should be reviewed accordingly.

In patients with shock, the current recommendation of WHO is to start intravenous fluid resuscitation with isotonic crystalloid solution, then reassess the patients' condition (vital signs, capillary refill time, hematocrit, urine output). The subsequent fluid management will depend on the patient's hemodynamic status. An IVF is classified as isotonic if it approximates the effective osmolality of plasma - that is 275-295 mosm/kg and as hypotonic if its osmolality is lower than the effective plasma osmolality (Choong 2007). Recently, so-called "balanced isotonic electrolyte solutions" such as Sterofundin ISO® and Plasmalyte 148® which contain sodium, electrolytes and osmolality/osmolarity* with values closer to plasma have been introduced. However, among the intravenous fluids closely resembling the osmolality of plasma, the most readily available and cheapest are 0.9 % NaCl and Ringer's lactate solution, which are recommended by the WHO (WHO 2009).

In patients with dengue, the critical period lasts for 24-48 hours only, and during this time, patients should be frequently monitored until the danger period is over. In patients with hypotensive shock, colloids may be the preferred choice over crystalloids if the blood pressure needs to be restored urgently. However, crystalloids and colloids have their own limitations when used in large quantities (WHO 2009). Please see Table 6 and 7 for examples of crystalloids and colloids and their characteristics.

*__Note:__ Osmolality and osmolarity both estimate the osmolar concentration in a solution and is called osmolality when the concentration is expressed as mOsmol/kg of water, and as osmolarity when it is expressed as mOsmol/L of solution. In dilute solutions such as in plasma, these two terms can be used almost synonymously because the differences are small.

Table 7. Composition and Effects of Selected Hypotonic and Isotonic Crystalloid Solutions compared to Plasma

Fluid	Na^+ (mmol/L)	K^+ (mmol/L)	Cl^- (mmol/L)	$HC0_3^-$ (mmol/L)	Osmolarity (mOsm/L)	Max. vol expansion (%)	Duratinn vol. expansion (hours)	Plasmatic half life (hours)	Possible Side Effects
Plasma	135–145	3.5–4.5	95–105	24–32	275–295	-	-	-	-
0.3%NaCl	51	0	51	0	95-102	0	0	0	Hyponatremia Encephalopathy
0.45%NaCl	77	0	77	0	142-154	0	0	0	Hyponatremia Encephlopathy
0.9% NaCl	154	0	154	0	285-308	20-25	1-4	0.5	Hyperchloremia Metabolic acidosis
Ringer's Lactate	130-131	5-5.4	111-112	28 (as acetate)	250-273	20-25	1-4	0.5	Hyperkalemia
Sterofundin ISO	140-145	5	127	24 (as acetate)	309	-	-	-	Hyperkalemia; hypernatremia
Plasmalyte 148	140	5	98	27 (as acetate) + 23 (as gluconate)	294-295	-	-	-	Hyperkalemia Metabolic alkalosis

Abbreviations: Na, sodium; K, potassium; Cl, chloride; $HC0_3^-$ Bicarbonate; NaCl, sodium chloride

Source: Varrier M, Ostermann M. Fluid Composition and Clinical Effects. Crit Care Clin. 2015 (31): 823–837.

Table 8. Characteristics of Selected Colloids (Dextran, Starch, Gelatin)

Fluids	Molec. wt (Kd)	Osmolality (mOsml/L)	Colloid Osmotic Pressure (mmHg)	Max. vol. expansion (%)	Duration of volume expansion (hours)	Plasma half life (hours)	Possible Side Effects
3,6,10% Hetastarch (HES)	450	300-310	23-50	100-200	8-36	50	Renal dysfunction
10% Pentastarch	280	326	23-50	100-200	12-24	2-12	Coagulopathy Pruritus
6% Tentra-starch (Voluven; Volulyte)	130	308		100	4-8		Anaphylac-toid reactions
10% Dextran70 3% Dextran 60, 6% Dextran 70	40 70	280-324 280-324	20-60 20-60	100-200 80-140	1-2 8-24	4-6 12	Anaphylactic Reactions Allergic Reactions Interference With blood crossmatching
Gelatin Succinylated and cross-linked (2.5, 3, 4% Urea-linked; 3.5% linked gelatins)	30-35	300-350	25-42	70-80	4-6	2-9	Reaction High calcium content (urea linked forms

The 2012 PPS Revised Guidelines on Fluid Management of Dengue Fever and Dengue Hemorrhagic Fever contains recommendations for fluid therapy for compensated shock and hypotensive shock (see **Appendix A).** The recommendations were based on the 2009 WHO Dengue guidelines for diagnosis, treatment, prevention and control (WHO 2009) and the 2011 WHO SEARO Comprehensive Guidelines (WHO 2011).

Question 4: Among Dengue patients without shock how effective are isotonic IVFs compared to hypotonic IVFs in reducing mortality?

Recommendation:

- There is insufficient evidence that the tonicity of the intravenous fluid has an effect on mortality in dengue patients without shock.
- Isotonic fluids can be used as maintenance for dengue patients without shock.
- The use of hypotonic IVF is associated with hyponatremia among hospitalized pediatric patients.

(Strong recommendation, based on low quality evidence)

Summary of Evidence

A systematic search of the literature did not yield studies that directly answered the clinical question. One systematic review (Wang, 2014) compared isotonic versus hypotonic maintenance intravenous fluids in hospitalized children. The review included eight randomized controlled trials (RCT) in a meta-analysis, treated as ten separate trials because two studies compared two fluids as two maintenance rates. The included studies differed in their risk of bias - three studies had unclear descriptions of their sequence generation, two studies were unclear in their allocation concealment, four of the studies used blinding methods, one study was assessed as having a high risk of incomplete outcome data, two studies did not report on the primary outcome, unpublished studies were not included.

A total of 855 hospitalized children aged 1 month to 17 years old who were a mix of surgical and medical cases were included in the 10 RCT's. Five trials included only surgical patients, 4 included both surgical and medical patients and 1 trial included only medical patients. The medical patients enrolled in the studies had a variety of conditions (respiratory, neurologic, infectious, and gastrointestinal), requiring maintenance intravenous fluid therapy. Fluids were considered isotonic if they had the same or near osmotic pressure as blood, these include 0.9% Saline, Hartmann's solution, or Ringer's solution and hypotonic fluids were considered as those with a lower osmotic pressure than blood, such as 0.45% Saline, 0.3% Saline, and 0.18% Saline. The primary outcome measure for the meta-analysis was the development of hyponatremia. Secondary outcomes were the development of severe or symptomatic hyponatremia (pNa <130 mmol/L), pNa level after IV fluid therapy, pNa changes after IV fluid therapy, hypernatremia (pNA > 145 mmol/L) and adverse events.

Table 9. Characteristics of Included RCTs Comparing Hypotonic with Isotonic Maintenance Fluids in Hospitalized Children (Wang 2014)

Study	Condition	Follow-up, h	Hypotonic			Isotonic		
			N	Age,[b] y	Solution	N	Age,[b] y	Solution
Brazel 1996	Surgical	≥72	7	Adolescent	0.3% S and 3% D; 0.18% S and 4% D	5	Adolescent	Hartmann's solution
Yung 2009a	Surgical and medical	≥12	15	4.7 (1.4–8.9)	0.18% S and 4% D	13	5.3 (0.9–12)	0.9% S
Yung 2009b	Surgical and medical	≥12	11	3.7 (1.5–14.7)	0.18% S and 4% D	11	15.4 (10.8–15.9)	0.9% S
Kannan 2010	Medical	≥24	56	4.0 (1.1–6.0)	0.18% S and 5% D at full rate	58	3.0 (1.0–7.0)	0.9% S and 5% D at full rate
	align	≥24	53	3.0 (0.8–5.5)	0.18% S and 5% D at 2/3 rate			
Neville 2010a	Surgical	≥8	31[c]	9.9 (2.0–15.0)	0.45% S and 5% D at half rate	31[c]	9.4 (1.0–14.9)	0.9% S and 5% D at half rate
Neville 2010b	Surgical	≥8	31	9.1 (0.9–14.9)	0.45% S and 2.5% D at full rate	31[c]	8.4 (0.6–14.9)	0.9% S and 2.5% D at full rate
Choong 2011	Surgical	≥24	130	9.2 ± 5.7	0.45% S and 5% D	128	9.2 ± 5.5	0.9% S and 5% D
Rey 2011	Surgical and medical	≥12	62[d]	4.7 (1.7–9.9)	30–50 mmol/L NaCl and 20 mmol/L KCl	63[d]	4.9 (2.0–10.6)	136 mmol/L NaCl and 20 mmol/L KCl
Saba 2011	Surgical and medical	≥8	21	8.9 (1.7–16.5)	0.45% S and 5% D	16	8.2 (2.8–14.3)	0.9% S and 5% D
Coulthard 2012	Surgical	≥16	41	11.5 (6.0–14.1)	0.45% S and 5% D	41	11.5 (4.3–13.9)	Hartmann's and 5% D

D, dextrose; KCl, potassium chloride; NaCl, sodium chloride; S, saline.
[a] Number of participants reported in the tables of baseline characteristics.
[b] Age is expressed as median (interquartile range), median (range), or mean ± SD.
[c] Including 2 participants with preexisting hyponatremia.
[d] Including 23 participants with preexisting hyponatremia.
[e] Including 18 participants with preexisting hyponatremia.

The following outcomes were evaluated:

- **Hyponatremia.** Seven trials were included in the meta-analysis for this outcome. The quality of evidence was graded as **low** due to unclear or lack of sequence generation, allocation concealment, and blinding and indirectness since the subjects of the studies were children who underwent surgery and other medical diseases, not dengue. The analysis of the studies showed that hypotonic IV fluids increased the risk for developing hyponatremia by more than 2 times (RR 2.24, 95% CI 1.52-3.31) compared to isotonic fluids.
- **Severe Hyponatremia.** The meta-analysis of this outcome included six studies. The quality of evidence was graded **low** due to unclear or lack of sequence generation, allocation concealment, and blinding and indirectness. The meta-analysis showed that hypotonic fluids increased the risk of severe hyponatremia by more than 5 times (RR 5.29, 95% CI 1.74-16.06) compared to isotonic fluids.

The following forest plots show the important outcomes in relation to hyponatremia.

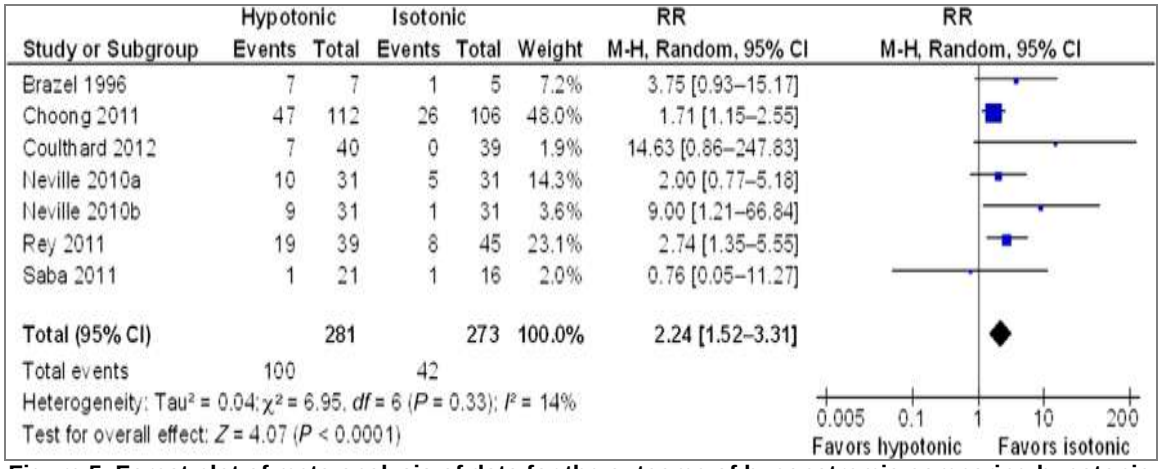

Figure 5. Forest plot of meta-analysis of data for the outcome of hyponatremia comparing hypotonic with isotonic IV maintenance fluids in hospitalized children (Wang 2014).

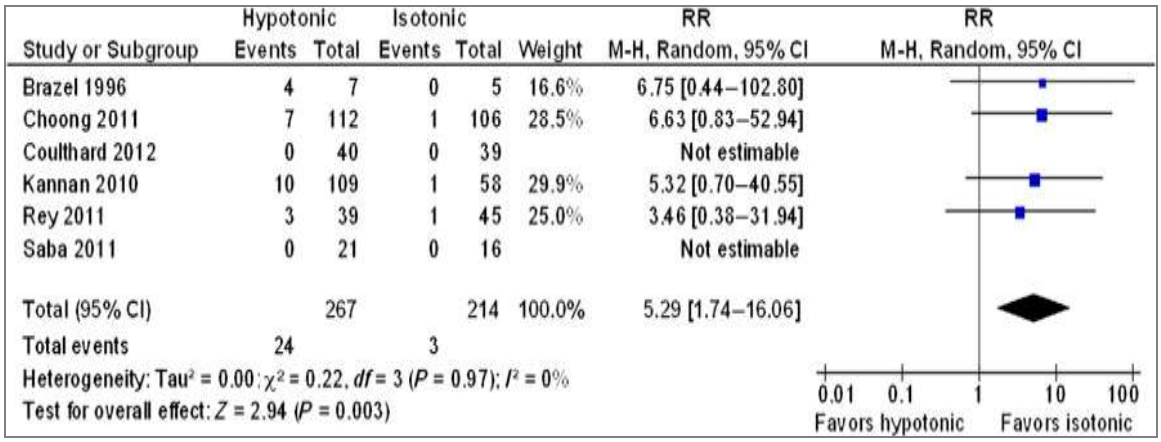

Figure 6. Forest plot of meta-analysis of data for the outcome of severe hyponatremia comparing hypotonic with isotonic IV maintenance fluids in hospitalized children (Wang 2014).

Adverse Effects

The review noted that there were two RCT's that reported adverse effects among its subjects. One study reported one subject who expired who was receiving isotonic fluids and was assessed to have acute respiratory distress syndrome; the subject had normal plasma sodium thought out the study. Another subject in the same study developed hyponatremic encephalopathy with seizures and stupor; this subject was receiving hypotonic IV fluids. In another study, two patients were reported to have new onset hypertension; these patients were receiving hypotonic fluids.

Consideration for recommendation development during Stakeholders Panel meeting:

- There is insufficient evidence to recommend using either hypotonic or isotonic fluids in decreasing the mortality of patients with dengue without shock based on evidence graded as **low** due to indirectness. The studies only determined the change of sodium during the maintenance period and mortality outcome of these two fluids was not considered. Furthermore, the populations included were surgical and medical patients. However, the Guideline Panel and Stakeholders believe that the same can be expected among pediatric cases of Dengue fever.
- Both hypotonic and isotonic fluids are available in the hospital. However, the studies included used fluids including 0.45% saline, which is not readily available.
- Hypotonic IV fluids used as maintenance can increase the risk of developing hyponatremia and monitoring plasma sodium level is needed if hypotonic fluids are administered.
- In the absence of evidence, the Stakeholders panel agreed that physicians can use the fluid management for patients admitted at hospital with compensated shock found in the 2012 PPS Revised Guidelines in management of dengue fever and dengue hemorrhagic Fever. (See **Appendix A**)
- After the Stakeholders panel meeting, it was brought to the attention of the Guideline Panel that there is a more recently published systematic review comparing isotonic

and hypotonic maintenance IVF in hospitalized children with a variety of medical and surgical conditions, none of which included dengue patients specifically (Padua 2015). Eleven RCTs were included in the meta-analysis, with an additional three trials aside from all eight trials in the review by Wang 2014. Findings in this more recent systematic review are consistent with the results of the review by Wang 2014 which showed that the risk of developing hyponatremia and severe hyponatremia is reduced with use of isotonic fluids compared to hypotonic fluid therapy in hospitalized children and should therefore be the initial fluids prescribed.

Question 5: Among Dengue patients with shock, how effective are colloidal IVFs compared to crystalloid IVFs in reducing mortality?

Recommendation:

- In dengue patients with shock, either crystalloids or colloids may be used for fluid resuscitation.
- There is insufficient evidence to say that the use of colloid IVF compared to crystalloids will have an effect on mortality.
- The use of colloids may be associated with more adverse reactions (e.g. bleeding, allergic reactions) compared to crystalloids.

***(Strong recommendation based on low and very low quality of evidence*)**

Summary of Evidence

One meta-analysis (Jalac, 2010) which included four randomized controlled trials (RCT) comparing the use of colloids and crystalloids in pediatric dengue shock syndrome (DSS) was identified. The included studies compared crystalloids which included 0.9% Saline and Ringer's Solution with colloids including Dextran 70, Gelatin, and Hydroxyethyl starch (HES) as initial fluids in the management of pediatric patients with DSS. Three of the included studies were conducted in Vietnam and one in Indonesia. Two studies were assessed as high quality (Wills 2005, Nhan 2001) while two studies were assessed as fair (moderate) quality, one did not state intention-to-treat analysis (Dung 1999) while another had unclear allocation concealment, did not state blinding, and did not state intention-to-treat analysis (Prasetyo 2008). Publication bias was suspected for the meta-analysis because only PubMed, Cochrane, and Herdin were searched and other databases might have been overlooked.

Subjects included 694 children ages 1 to 15 years old who initially presented with dengue shock syndrome or DHF Grade III or IV based on WHO guidelines. Two studies randomized patients to either 0.9% Saline, Ringer's Solution, Dextran 70, or Gelatin (Dung 1999 and Nhan 2001); one study stratified patients into two groups according to the pulse pressure at admission with one having patients with shock of moderate severity (pulse pressure >10 and ≤20 mm Hg) randomly assigned to receive Ringer's solution, dextran, or HES and the other group with severe shock (pulse pressure ≤10 mm Hg) randomly assigned to receive either dextran or HES (Wills 2005); the fourth study randomized patients to HES or Ringer's (Prasetyo 2008). The study by Dung 1999 administered fluids at 20ml/kg for 1 hr while Wills 2005 administered fluids at 15ml/kg for 1 hr, both studies then administered 10ml/kg for the 2nd hr; in Nhan 2001 the study fluids were initially given at 20ml/kg for 1 hr for DHF Grade III patients and 20ml/kg for 15min for DHF Grade IV patients, then 20ml/kg over the following hour; Prasetyo 2008 administered 20ml/kg to all patients as initial fluid resuscitation. Outcome measures analyzed were the need for diuretics, the need for rescue fluids, the recurrence of shock, the decrease in hematocrit and pulse rate from baseline, and the total volume of fluids given, no mortality outcome was measured. These studies were unable to demonstrate a clear benefit of any 1 of the 4 fluids in dengue shock management.

Table 10. Characteristics of Included RCTs in the Systematic Review Comparing Use of Crystalloids and Colloids in Dengue Patients with Shock (Jalac 2010)

Author, Year	Study Population	Intervention	Outcomes	Adverse Reactions
Nhan 2001[7]	230 Vietnamese children clinically diagnosed DHF DHF grade III = 222 DHF grade IV = 8 1-15 years old	Study fluids Lactated Ringer's solution, isotonic saline, dextran, gelatin Fluid rate DHF grade III: 20mL/kg for 1 hr DHF grade IV: 20ml/kg for 15min, then 20mL/kg over the following hour	Data presented are those of DHF grade III patients only: PPRT, reshock rate, time to 1st episode of reshock, change from baseline of hematocrit and pulse rate, volume of fluid infused, requirement for rescue fluid, volume of rescue fluid used, requirement for diuretic, mortality	None stated
Wills 2005[8]	512 Vietnamese children with clinical DSS Moderate shock = 383 Severe shock = 129 2-15 years old	Study fluids Lactated Ringer's solution, starch, dextran Fluid rate 15mL/kg for 1 hr, then 10mL/kg for the 2nd hr	Change from baseline of hematocrit; total volume of rescue fluid used after initial resuscitation, total volume of fluid given, requirement for further fluid resuscitation, requirement for diuretic, mortality, length of hospital stay, depth of pleural effusion, new bleeding after study entry, clinical fluid overload, volume of ascites	Allergic type reactions, transient high fever and rigors without cardio-respiratory compromise; urticarial rashes
Dung 1999[9]	50 Vietnamese children with clinical DSS 5-15 years old	Study fluids Lactated Ringer's solution, isotonic saline, dextran, gelatin Fluid rate 20mL/kg for 1 hr, then 10mL/kg for the 2nd hr	Change from baseline of hematocrit, cardiac index, pulse rate and pulse pressure, requirement for further fluid resuscitation, requirement for diuretic, duration of shock, episodes of reshock, mortality	None stated
Prasetyo2008[6]	39 Indonesian children with clinical DSS 1-13 years	Study fluids Lactated Ringer's solution, gelatin Fluid rate 20mL/kg as initial volume of fluid resuscitation	Change from the baseline of hematocrit, hemoglobin, pulse rate and pulse pressure; total volume of fluid given, episodes of reshock, mortality	Adverse reactions in coagulation, liver and renal functions and acid-base equilibrium; severe allergic type reactions

DHF: dengue hemorrhagic fever
DSS: dengue shock syndrome
PPRT: pulse pressure recovery time

The following parameters were evaluated:

- **Recurrence of shock after the initial fluid resuscitation.** Three randomized controlled trials were included in the meta-analysis. There was no significant difference between crystalloids and colloids in decreasing the risk for the recurrence of shock (RR 0.92, 95% CI 0.62 to 1.38). The quality of evidence is **very low** due to indirectness since the recurrence of shock may not always lead to mortality, imprecision due to the wide confidence interval thus there is still a possibility of either benefit or harm, and publication bias.
- **Patients who needed rescue colloids after the initial fluid resuscitation.** Two randomized controlled trials were pooled for this outcome. The need for rescue fluids did not differ significantly (RR .90, 95 % CI 0.70 to 1.16) between crystalloids and colloids. The quality of evidence is **very low** due to indirectness since the need for rescue colloids after the initial fluid resuscitation may not always lead to mortality, imprecision since there is still a possibility of definite benefit as confidence interval is wide, and publication bias**.**
- **Number of patients given diuretics after fluid resuscitation.** In the two randomized controlled trials that were included in the meta-analysis, there was no significant difference between crystalloids and colloids in the number of patients given diuretics after fluid resuscitation (RR =1.17, 95% CI 0.84 to 1.64). The quality of evidence is **very low** due to indirectness since the need for diuretics may not always lead to mortality**,** imprecision since there is still a possibility of definite harm, and publication bias.
- **Total volume of intravenous fluids given**. There were three randomized controlled trials pooled for this outcome. There were 0.80 times more fluids given to children using crystalloids than colloids but this is not significant (WMD 0.80 more, 95% CI -1.68 to 3.28)**.** The quality of evidence is **very low** due to indirectness since total volume of intravenous fluids given is a surrogate outcome only and does not translate to mortality, imprecision since there is still a possibility of either benefit or harm as confidence interval is wide, and publication bias

- **Decrease in hematocrit levels of patients 2 hours after fluid resuscitation**. Three randomized controlled trials were included in the meta-analysis. There was significant improvement from baseline hematocrit levels of patients who were given colloids. The decrease in hematocrit levels of patients 2 hours after fluid resuscitation is 8 times fewer among those given crystalloids compared to those given colloids (WMD 7.87 fewer, 95%, CI -8.53 to -7.22). The quality of evidence is **very low,** there is significant heterogeneity with 99% variability, indirectness since decrease in hematocrit levels is a surrogate outcome only and does not translate to mortality, and publication bias.
- **Decrease in pulse rate (beats /min) of patients 2 hours after fluid resuscitation.** Two randomized controlled trials were pooled for this outcome. There was significant improvement from the baseline pulse rate levels**.** Subjects who given colloids had 3 times decrease in pulse rate 2 hours after fluid resuscitation than those on crystalloids (WMD -3.37,95% CI -5.94 to - 0.8). The quality of evidence was **low** since decrease in pulse rate is a surrogate outcome only and does not translate to mortality, and publication bias.

Mortality:

- There was one death reported in the study by Wills 2005, a child who received starch who died of profound shock and gastrointestinal bleeding. All the other patients in this trial and in the other trials included in the meta-analysis made a full recovery and were discharged.

Adverse Events:

- **Bleeding:** In the study by Nhan 2009, bleeding developed in two patients in the colloid group but none in the crystalloid group. Of the two children who developed bleeding, one child who was given gelatin developed severe epistaxis requiring blood transfusion and another child given dextran developed a large hematoma at the site of minor trauma. In the study by Wills 2005, there was no difference in the development of any bleeding episodes of any severity in the groups: 32 of 193 patients (16.6%) in the dextran group, 33 of 191 patients (17.3%) in the starch group and in 20 of 128 (15.6%) in the Ringer's lactate group. Among those with bleeding, there was no difference in those requiring transfusion among the three groups.
- **Fluid overload**: In the study by Nhan 2001, the frequency requiring furosemide was similar among those who received colloids compared to crystalloids: 13.5% in those who received dextran or gelatin compared to 18% in those who received Ringers lactate or normal saline. In the study by Wills 2005, there were no differences among the fluid treatment groups in the development of clinical fluid overload with 36.8% in the dextran 32.9% in the starch group and 30% in the Ringer's lactate group. In addition, the frequencies of patients requiring furosemide therapy were similar in the groups compared: 30% in the dextran group, 29.3% in the starch group, and 19.5% in the Ringer's lactate group. In the study by Dung 1999, no patients in any of the groups required diuretic therapy for clinically detected fluid overload. Prasetyo 2009 did not mention fluid overload in their report.
- **Allergic reactions:** No allergic reactions were noted in the crystalloid group in any of the trials. In the study by Nhan 2009, 6 patients, (5 given gelatin and 1 dextran) developed allergic reactions and in all cases, the fever and chills resolved after paracetamol. In the study by Wills 2005, 15 of 193 patients (8%) in the dextran group developed severe allergic reactions within 6 hours of fluid infusion. The allergic reactions were described as fever and chills but without cardiorespiratory

compromise and responded to symptomatic treatment alone. In addition, 1 of 191 (0.5%) developed urticarial rash in the starch group. There were no dermatologic problems or other allergic reactions reported in the other two trials.

- **Other adverse events:** In the study by Prasteyo 2009, no significant difference between the groups were observed in blood coagulation, impaired liver and renal function, and in acid-base equilibrium. However, actual data was not reported.

Consideration for recommendation development during Stakeholders Panel meeting:

- Colloids decreased the hematocrit and pulse rate of children with DSS after the first 2 hours of fluid resuscitation. However, there is no significant advantage of colloids was found over crystalloids in reducing the recurrence of shock, the need for rescue colloids, the total amount of fluids, the need for diuretics, and in reducing mortality.
- For the majority of patients with less severe disease, the type of fluid used for resuscitation may not actually matter.
- Of the four fluids evaluated, Lactated Ringer's Solution performed the least well, which suggest that the simple, widely available 0.9% saline maybe the crystalloid of choice for resuscitation of the majority of patients with dengue shock syndrome.
- Availability and cost of the type of fluids, crystalloids or colloids should be taken into account and it is plausible that factors such as comorbidity, acute illness severity, and ICU-acquired complications have a more powerful influence on mortality than does resuscitative fluid.
- Between 0.9% saline and Ringer's solution, 0.9% saline showed more benefits in dengue shock syndrome. Though colloids have better benefit with cardiovascular stability, these solutions are not readily available in all institutions and are expensive. There are also reports of allergic reactions of these colloidal fluids.

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CHAPTER 4

ROLE OF BLOOD PRODUCT TRANSFUSION IN DENGUE

Bleeding in dengue may be due to vasculopathy, thrombocytopenia, platelet dysfunction, and deranged coagulation (Srichaikul 2000; WHO 2009). In some cases, bleeding may result from liver failure (Academy of Medicine of Malaysia 2000). When major bleeding occurs, it is almost always associated with profound shock since this, in combination with thrombocytopenia, hypoxia and acidosis, can lead to multiple organ failure and disseminated intravascular coagulation. Disseminated intravascular coagulation (DIC) leads to severe hemorrhage causing the hematocrit to decrease (WHO 2009). A physician should always be on alert to the possibility of concealed bleeding if the patient continues to deteriorate with a serial decrease in the hematocrit in spite of the intravenous fluids. Massive bleeding may also occur without prolonged shock in instances when acetylsalicylic acid (aspirin), ibuprofen or corticosteroids have been taken (WHO 2009).

Blood products are not routinely used in dengue fever unless there is profuse bleeding or clinical deterioration refractory to vigorous fluid resuscitation. In such cases, blood transfusion is life saving and should be given as soon as severe bleeding is suspected or recognized (WHO 2009). The use of red cell products such as fresh whole blood and packed red cells are the components of choice for those with massive bleeding especially those emanating from the gastrointestinal tract and/or vagina in adult females. (WHO 2009). The practice of platelet concentrate and plasma transfusion for severe bleeding remains controversial and may further exacerbate fluid overload (WHO 2009). If hemorrhage persists despite red cell replacements with fresh whole blood or fresh-packed cells or if DIC is suspected, some clinicians may consider giving plasma products such as fresh frozen plasma or cryoprecipitate (WHO 2009). DIC should be suspected in cases of severe bleeding associated with low or rapid decline in platelet count, prolongation of clotting times, such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT), presence of fibrin-degradation products in plasma, and low levels of fibrinogen and coagulation inhibitors such as antithrombin III (Wada 2012)

Inappropriate transfusion of platelet and fresh frozen plasma may cause fluid overload (WHO 2009). Prophylactic transfusion of plasma products including platelet concentrate in those without signs of bleeding is unnecessary and is strongly discouraged due to the possibility of allergic reactions, transfusion-related acute lung injury, and transmission of other diseases.

The following table shows the recommended dose and indication for transfusion of the different blood products in dengue based on various guidelines. Among these blood products, only the transfusion of red cell products, either fresh whole blood (FWB) or packed red blood cells (PRBC), have been recommended by the WHO in patients with dengue presenting with significant bleeding.

Table 11. Blood products in Dengue Fever

Blood product	Dose	Indication	Remarks
Fresh whole blood (FWB) *	10-20 ml/kg	Persistent and/or severe overt bleeding in the presence of unstable hemodynamic status; Unstable hemodynamic status or refractory shock with decreasing Hct despite adequate fluid administration	Decrease in Hct together with stable hemodynamic status and adequate urine output indicates hemodilution and/or reabsorption of extravasated fluids and does not warrant blood transfusion. Monitor hemodynamic status after blood transfusion; repeat transfusion if there is further blood loss or no appropriate rise in Hct after blood transfusion.
Packed red blood cells (PRBC)*	5-10cc/kg	Persistent and/or severe overt bleeding in the presence of unstable hemodynamic status; Unstable hemodynamic status or refractory shock with decreasing Hct despite adequate fluid administration	As above. PRBC is preferred over FWB if fluid overload is present
Fresh Frozen Plasma (FFP)	10 -20 cc/kg	Massive bleeding not responsive to transfusion of fresh whole blood or fresh-packed cells; in cases of coagulopathy with bleeding or suspected or confirmed DIC	Do not give prophylactic FFP transfusions in the absence of bleeding. FFP transfusion leads to fluid overload because repeated and large volume (40-50ml/kg) are needed for correction of coagulopathy FFP transfusions do not produce sustained changes in the coagulation status and do not reduce the bleeding outcome in patients with DHF/DSS.
Cryoprecipitate	1 u/ 5kg	Massive bleeding not responsive to transfusion of fresh whole blood or fresh-packed cells; in cases of coagulopathy with bleeding or suspected or confirmed DIC	Do not give prophylactic cryoprecipitate in the absence of bleeding. Cryoprecipitate contains fibrinogen, von Willebrands factor, Factors 8 and 13; less risk of fluid overload compared to FFP
Platelet concentrate	1 unit/10 kg	In patients with platelet count ≤ 10,000/mm^3. associated with systemic massive bleeding or prolonged shock with bleeding not responsive to red cell products (FWB or PRBC) or plasma products (FFP or cryoprecipitate)	Prophylactic platelet transfusion is not recommended in the absence of bleeding even at levels ≤ 20,000/mm^3.

Source: WHO 2009; Kaur 2014 ; Ministry of Health-Sri Lanka 2010

* Fresh whole blood or fresh red cells are preferable because stored blood loses 2,3 DPG, low levels of which impede the oxygen-releasing capacity of hemoglobin, resulting in functional tissue hypoxia.

Question 6: Among patients with thrombocytopenia because of dengue, how effective is prophylactic platelet transfusion in improving platelet count, preventing hemorrhage, and reducing mortality?

Recommendation:

- There is insufficient evidence to say that prophylactic platelet transfusion in patients with minimal or no active bleeding will improve platelet counts, prevent hemorrhage and reduce mortality.
- Children with dengue who have platelet count <50,000/mm^3 with minimal or no active bleeding should not be given prophylactic platelet transfusion.

(Strong recommendation, based on moderate to very low quality evidence)

Summary of Evidence

There were a total of three trials that addressed this question: one randomized trial (Assir 2013) and two observational trials (Lye 2009; Prashanta 2014). All of the included trials were conducted in adults; there were no trials in children. All three trials compared patients given platelet transfusion with those who were not.

Randomized trial

One randomized trial enrolled 87 adult patients aged 14 years and above with dengue, platelet count below 30,000/µL, and with no bleeding or mild bleeding (WHO grade 1 or 2) who were admitted in a single hospital in Pakistan (Assir 2013). Forty-three patients were randomized to receive single donor platelet transfusion and 44 were randomized to no transfusion. The range of platelet count in those given platelet transfusion was 8,000/µL to 15,000/µL and in those not given platelet transfusion was 9000/µL to 17,700/µL. The primary outcome measured was mean post-transfusion platelet increment at 24 hours and 72 hours in both groups. Secondary outcomes measured for both groups were progression to severe bleeding (WHO grade 3 and 4), any new onset bleeding, time to cessation of bleeding, and any adverse events, including death. At one hour post-transfusion, post-transfusion platelet increment and the proportion of responders, defined as post-transfusion platelet increment ≥ 10,000/µL and/or corrected count increment ≥ 5,000/µL was determined but for the treatment group only. Only 15 (36.5%) patients were responders, 3 patients (7%) showed a decrease in platelet counts, and 22 (53.6%) were nonresponders. Comparison of the two groups showed the following results:

- **Mean platelet count 24 hours after transfusion:** The quality of the graded as **moderate** due to indirectness (study population were adults). Mean post-transfusion platelet increment 24 hours after platelet transfusion was significantly higher compared to those who did not receive any platelet transfusion (34,780 ±43,820 vs 4,280 ±10,360; p<0.001).
- **Mean platelet count 72 hours after transfusion:** The quality of evidence was graded as **moderate** due to indirectness. Mean post-transfusion platelet increment 72 hours after platelet transfusion remained significantly higher compared to those who did not receive any platelet transfusion (75,430 ±69,465 vs 32,840 ±30,900; p<0.001).
- **Bleeding:** The quality of evidence was **moderate**. None of the patients without bleeding at baseline had new onset bleeding during the study period in the two groups. Among patients with bleeding at baseline, progression to WHO grade 3 was

observed in one patient who received platelet transfusion and none in the control group. This implies that platelet transfusion did not prevent progression to bleeding.

- **Cessation of bleeding:** The quality of evidence was **moderate.** The mean time to cessation of bleeding was 31.6 hours in those given platelet transfusion and 25.2 hours in the control group, but results were not statistically significant (p=0.346). This implies that platelet transfusion did not shorten time to cessation of bleeding.
- **Mortality:** The quality of evidence was **moderate.** There were two deaths in the group given platelet transfusion and none in the control group. One death was due to development of transfusion-related acute lung injury following platelet transfusion. The other mortality was a case later diagnosed to have liver cirrhosis whose death was attributed to multifactorial causes, including anaphylactic shock, bleeding from esophageal varices due to liver cirrhosis and old age.
- **Transfusion reaction**: The quality of evidence was **moderate.** Three patients who were given platelet transfusion developed severe anaphylactic reaction and hypotension.

Non-randomized clinical trials

There were two retrospective cohort studies that compared prophylactic platelet transfusion with no transfusion. One trial enrolled 256 adult dengue patients without bleeding whose platelet count was below 20,000/μL admitted in a tertiary hospital in Singapore (Lye 2009). Of the 256 patients, 188 were given platelet transfusion while 68 were not. The platelet count ranged from 7,000/μL to 19,000/μL in those given platelet transfusion and 8,000/μL to 19,000/μL in those not given platelet transfusion. The other study was conducted in a referral hospital in India and compared adult dengue patients who are Jehovah's witnesses (n=28) who did not receive any platelet transfusion and patients who are not Jehovah's witnesses and received prophylactic platelet transfusion (n=23) (Prashanta 2014). The platelet count ranged from 4,000/μL to 37,000/μL in those given platelet transfusion and 6,000/μL to 38,000/μL in those not given platelet transfusion.

- **Median time to platelet count >50,000/μL:** The quality of evidence was **very low** due to study design (nonrandomized trial), indirectness (adults and difference in outcome), and imprecision. In the study by Lye 2009, the median time to recovery of the platelet count to >50,000/μL was 3 days in both groups. In the study by Prashanta 2014, the median time to recovery of the platelet count to >50,000/μL was 4.43 ± 4.67 days in those given platelet transfusion and 2.57 ± 3.83 days in those patients not given transfusion. Pooled results showed that there was no significant difference in the median time to platelet recovery in the two groups (Mean difference 0.96, 95% CI -0.86 to 2.78; p=0.30). This implies that prophylactic platelet transfusion does not hasten platelet recovery.
- **Median length of hospital stay:** The quality of evidence was **very low** due to study design (nonrandomized trial), indirectness (adults and difference in outcome), and imprecision. In the study by Lye 2009, the median length of hospital stay was 6 ± 13.9 days in those who were given platelet transfusion and 5 ± 6.2 days in the control group. In the study by Prashanta 2014, the median length of hospital stay was 5.13 ± 5.84 days in those who were given platelet transfusion and 3.68 ± 4.63 days in those patients not given transfusion. Pooled results showed that there was no significant difference in the length of hospitalization in the two groups (Mean difference 1.19, 95% CI -0.71 to 3.08; p=0.22). This implies that prophylactic platelet transfusion does not reduce hospital stay.

- **Bleeding**: The quality of evidence was **very low** due to study design (nonrandomized trial), indirectness (adults and difference in outcome), imprecision, and other inherent bias that could result in confounding. In the study by Lye 2009, severe bleeding leading to disseminated intravascular coagulation and death subsequently occurred in one patient (0.5%) of 188 given prophylactic platelet transfusion compared with 2 (2.9%) of 68 patients not given platelet transfusion, both of which were mild and did not require any intervention. In the study by Prashanta 2014, there was no bleeding observed in both groups. Pooled data showed an odds ratio of 0.18 (95% CI 0.02 -1.96; p=0.16). This result suggests that prophylactic platelet transfusion did not reduce subsequent occurrence of bleeding.
- **Mortality:** The quality of evidence was **very low** due to study design (nonrandomized trial), indirectness (adults and difference in outcome), imprecision, and other inherent bias that could result in confounding. One patient died in the group given prophylactic transfusion and none in the control. The patient who died was known to have peptic ulcer disease and presented with severe gastrointestinal bleeding leading to disseminated intravascular coagulation and acute renal failure. Pooled result showed that prophylactic platelet transfusion did not appear to reduce risk for death (OR 1.10, 95% CI 0.05-26.57; p=0.96).
- **Adverse effects:** One patient developed an allergic reaction to FFP during the study. There were no adverse events reported for those given isotonic saline.

Table 12. Summary of Studies on Prophylactic Platelet Transfusion in Dengue Patients

Study ***(Study Design)***	**Study Period**	**Patients (N)**	**Location**	**Outcome determined**	**Remarks**
Assir 2013 *RCT, open*	Not reported	Adults ≥ 14 yrs old with DF or DHF based on WHO criteria with platelet count <30,000/uL and no or mild bleeding (N=87)	Dengue unit of a Hospital in Pakistan	Efficacy of prophylactic platelet transfusion in dengue patients with thrombocytopenia	No lab confirmation of dengue; Only adults were included
Lye 2009 *Retrospec-tive cohort*	2004	Adults 17-57 yrs old with DF or DHF based on WHO criteria and serology or PCR confirmed with platelet count <20,000/uL, w/ or w/o bleeding (N=256)	Infectious Disease unit of a Hospital in Singapore	Efficacy of prophylactic platelet transfusion in dengue patients with thrombocytopenia	Only adults were included
Prashan-tha 2014 *Retrospec-tive cohort*	June 2009 – Dec 2010	Adults 18-45 yrs old with DF, thrombocytopenia < 50,000/uL, and no active bleeding (N=51)	Referral center for Jehovah's Witnesses in India	Efficacy of prophylactic platelet transfusion in dengue patients with thrombocytopenia	No lab confirmation of dengue; Only adults were included

Consideration for recommendation development during Stakeholders Panel meeting

- There is insufficient evidence to recommend prophylactic platelet transfusion in children with dengue who have low platelet counts but who have no significant bleeding.
- There is insufficient data to show that platelet transfusion prevents progression to severe bleeding or reduces risk of subsequent bleeding, hastens platelet recovery, reduces hospital stay, or decrease risk of mortality.

Question 7: Among Dengue patients with significant bleeding, how effective is plasma transfusion in controlling bleeding and reducing mortality?

Recommendation:

- Among dengue patients with significant bleeding, there is insufficient evidence that plasma transfusion has an effect on controlling bleeding and reducing mortality.
- The effect of plasma transfusion on platelet count recovery is not significant in dengue patients with bleeding.
- In children exhibiting signs of disseminated intravascular coagulopathy (DIC), plasma transfusion may be considered.

(Strong recommendation based on low quality evidence)

Summary of Evidence

Only one randomized controlled trial (Sellahewa 2008) that determined whether fresh frozen plasma was effective in adult dengue patients diagnosed with dengue was identified. There were no randomized trials in children. The included study was a randomized, double blind trial conducted in Colombo, Sri Lanka and enrolled adult patients with clinical symptoms of dengue and serological confirmation (positive dengue specific IgM by ELISA or haemagglutination inhibition tire of ≥ 1:2560) with platelet counts between 10,000 to 40,000/mm^3. Patients with platelet counts below 10,000/mm^3, dengue shock syndrome, or were seriously ill were excluded. None of the patients were reported to have severe bleeding. A total of 109 dengue patients who fulfilled the inclusion criteria were randomized to receive either one intravenous infusion of 3 units (600ml) of fresh frozen plasma (FFP) over 90 minutes (n= 53) or equal volume of isotonic saline infused over the same period. (n=56) The primary outcome measures were the platelet counts at 12, 24, and 48 hours, post-intervention. Any adverse effects were also recorded.

Table 13. Summary of Studies on Plasma Transfusion in Dengue Patients

Study ***(Study Design)***	**Study Period**	**Patients (N)**	**Location**	**Outcome determined**	**Remarks**
Sellahewa 2009 *RCT*	Nov 2005 – Aug 2006	Adults with clinical DF and serologically confirmed with platelet count <40,000/mm^3 with or without bleeding (N=109)	National hospital in Sri Lanka	Efficacy of FFP transfusion in dengue patients with throm bocytopenia	Only adults were included

The following parameters were evaluated:

- **Mean platelet count 12 hours after transfusion:** The quality of the graded as **moderate** due to indirectness (study population were adults with no bleeding; outcomes were different). The mean platelet count 12 hours post-intervention was significantly higher in those who received FFP compared to those who received isotonic saline (31.2 ± 37.1 vs 33.1 ±11.0; p=0.04). This may indicate that in dengue patients with thrombocytopenia, FFP infusion may result in an increase in platelet count early in the disease when the platelet count is decreasing.

- **Mean platelet count 24 hours after transfusion:** The quality of the graded as **low** due to indirectness (study population were adults with no bleeding; outcomes were different) and imprecision. Twenty-four hours following intervention, the mean platelet count was higher in those who received FFP compared to those who received isotonic saline (49.7 ± 44.7 vs 40.2 ±30.1; p=0.26) but the difference was not statistically significant
- **Mean platelet count 48 hours after transfusion:** The quality of the graded as **low** due to indirectness and imprecision. The mean platelet count 48 hours post-intervention continued to be higher in those who received FFP compared to those who received isotonic saline (105.1 ± 64.9 vs 84.7 ±62.8; p=0.12) but the results were not statistically significant. This may indicate that in dengue patients with thrombocytopenia, FFP infusion may be useful only early in the disease but may have no benefit in the later stages of disease.
- **Shock:** There were 3 patients who developed shock during the study however, it was not mentioned under what intervention group these patients belonged.
- **Mortality:** This study did not measure this outcome specifically. However, there were no deaths among the patients enrolled in the study. There is no evidence that FFP reduced mortality in dengue patients with severe bleeding.
- **Adverse effects:** One patient developed an allergic reaction to FFP during the study. There were no adverse events reported in those given isotonic saline.

Consideration for recommendation development during Stakeholders Panel meeting:

- There is insufficient evidence to recommend FFP transfusion in children with dengue who have severe bleeding. It is not known if FFP will reduce bleeding or reduce mortality in dengue patients with severe bleeding.
- The potential adverse effects of FFP were also higher in those given FFP compared to those given isotonic saline, such as increased risk for allergic reaction and volume overload.
- During the Stakeholder meeting the Philippine Society of Hematology and Blood transfusion raised their concern that although transfusion of plasma products (fresh frozen plasma, cryoprecipitate or platelet concentrate) should not be given routinely in dengue patients, however for those with significant bleeding and/or signs of DIC, transfusion of plasma products should be considered and left to the discretion of the physician. This is also consistent with the recommendation of the Ministry of Sri Lanka (2010).
- The other stakeholders mentioned that not all bleeding in patients with dengue is caused by DIC. DIC should be clearly defined (definition of DIC is included in the Glossary of terms).

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CHAPTER 5

INSECT REPELLENTS IN DENGUE

Repellants play a very important role in the prevention of mosquito-borne infections, including dengue. The US Environmental Protection Agency or EPA, classifies repellents under pesticides (US Environmental Protection Agency 2011). These are substances or mixture of substances intended for preventing, destroying, repelling or reducing any pests. These substances do not necessarily have to kill the insects but may also just make the user less attractive to them. Repellants make take any form. Although most people think that this only includes substances you apply over skin, this is not so. Skin applied repellants are the most widely used since they stay on regardless of movement. Repellants may include other forms like clip on or sticker forms that we use like lanterns, torches, tabletop diffusers, candles, oils and coils. All products need to be approved before release for use among consumers because of effectiveness and safety issues.

There are several repellants available for use, some FDA- approved for this purpose. N,N-diethyl-m-toluamide (DEET) and Dimethylphthalate (DMP) are two that are chemically synthesized and have been effective in dispelling blood-sucking insects, mites, ticks and leeches (Tyagi 1998). These two, though highly effective, have disadvantages like development of tolerance in mosquitoes, toxic reactions, ill effects in the environment, effect on other non-target organisms in the surroundings and damaging effects on plastics and synthetic fabrics. (Tyagi 1998; Wu 2013; Makhaik 2005). Thus a search for more naturally available effective repellants became necessary.

Traditionally, plant-based repellants have been used for generations. This is because naturally occurring extracts appear to be less harmful than synthetic ones (Maia 2011). There is however a variety of ways by which such substances are tested and not everything goes through the WHO Pesticide Evaluation Scheme guidelines for repellent testing. There is a clear need to standardize rules and regulations about use of these repellants.

Chemicals being used for this purpose fall into several categories, including repellents, feeding deterrents, toxins, and growth regulators. Most can be grouped into five major chemical categories: (1) nitrogen compounds (primarily alkaloids), (2) terpenoids, (3) phenolics, (4) proteinase inhibitors, and (5) growth regulators. Although most of these substances deter phytophagous insects, most also evolved into being effective against hematophagous insects as well thus its use against virus-harboring mosquitos that transmits infections.

Plants commonly produce volatile “green leaf volatiles” when leaves are damaged in order to deter herbivores, and several authors have shown strong responses of mosquito odor receptors to this class of volatiles including geranyl acetate and citronella. Many however of these plant volatiles are deterrent or repellent because they have high vapor toxicity to insects thus the use in preventing infections that results from insect bites. There are, however, no studies that directly show how much of these repellants really lower incidence rates of actual infections caused by these insects.

The CDC recommends that only EPA-approved products are used (CDC 2015). One should therefore seek for only EPA-approved products as a choice for repellants. There

are currently products in the market that have no EPA approval and whose main ingredients appear to pose minimal risk for human health. At the same time, there are also minimal studies to show effectiveness of such products. Products available in the market that are not EPA-registered are the following: citronella oil, cedar oil, geranium oil, peppermint and peppermint oil and soybean oil.

Question 8: Among populations at risk for Dengue transmission, how effective are citronella-based repellents compared to DEET-based repellents in reducing the incidence of Dengue?

Recommendation:
There is insufficient evidence to say that use of citronella-based repellents is more effective than DEET-based repellents in reducing dengue transmission.

(***Strong recommendation based on very low quality evidence)***

Summary of Evidence

No studies comparing citronella-based and DEET-based insect repellants in reducing the incidence of dengue were found after a systematic search of the literature. Only studies on repellency (mosquito bite prevention) were found.

Ten repellency studies evaluating various substances, including citronella oil and DEET, against various mosquito species, including *Aedes aegypti*, were found. Three studies compared citronella against DEET in repelling mosquitoes from human volunteers (Semmler 2014, Tawatsin 2001, Thornsell 1998), one study compared citronella against DEET in terms of mosquito avoidance (Boonyuan 2012), four studies evaluated the repellent activity of citronella oil but were non-comparative (Nuchuchua 2009; Trongtokit 2005; Tyagi 1998; Wu 2013), one study evaluated candles containing citronella (Muller 2008) and one study evaluated lethal concentration (Makhaik 2005). The studies were heterogenous in their sources of citronella oil (i.e., *Cymbopogon nardus, Cymbopogon winterianus, Cymbopogon flexuous),* mosquito species tested, citronella formulations and concentrations used, in their field and/or laboratory settings, and in their evaluation of repellent activity.

Four comparative studies evaluated citronella oil against DEET in repellant activity against mosquitoes. One study (Semmler 2014) compared 15 plant extracts, including *Cymbopogon nardus* extracts, and DEET on biting activity of *Aedes aegypti* mosquitoes. The hands of 5 volunteers were applied with 0.25 and 1% test solution and were then exposed to the mosquitoes; repellent failure was defined to occur as soon as three mosquitoes had sucked blood at the impregnated skin within 3 min after the first exposure. *Cymbopogon nardus* at 0.25% dilution and 1% dilution showed no repellancy compared to DEET 10% dilution which showed full protection within 3 minutes. The evidence was graded **very low.** Another study (Tawatsin 2001) evaluated volatile oils from 4 plant species including citronella grass (*Cymbopogon winterianus*) compared to DEET with and without the addition of vanillin against three mosquito vectors - *Aedes aegypti, Anopheles dirus* and *Culex quinquefasciatus*. The repellancy rate of the volatile oils was evaluated using the human-bait technique of the WHO on 3 volunteers; the time between application of the repellants and the second successive bite was recorded as the protection time. Volunteers were placed in a large room and exposed to the mosquitos for 10 minutes; evaluation was done by catching the mosquitos that landed on or bit the volunteer's leg. Protection time from *Aedes aegypti* for citronella without vanillin was 3 hrs and citronella with vanillin was 6.5 hrs; protection time for DEET with and without vanillin was 8 hrs. The results of large room evaluations confirmed the responses for each repellent treatment obtained under cage conditions. The evidence

was graded **very low.** The third comparative study (Thorsell 1998) evaluated various natural products including citronella oil against DEET in repellency against *Aedes aegypti* in the laboratory and also in the field. The hands of the test person were covered with special gloves with an opening where the extract was applied, then exposed in a mosquito cage where the number of sucking mosquitos was counted. A field test was also carried out where *Aedes communis* and *A. cinereus* were present. The number of blood sucking mosquitoes on the test hand at 0 hours, 0+4 hours, 0+4+6 hours and 0+4+6+8 hours was counted, *t*, and corresponding mosquito numbers on the control hand were noted, *c*; the repelling effect at the different occasions was expressed as 100(1-t/c)%. Average efficacy of citronella extract with 1.2 mg/cm concentration of skin ranged from 31.9 ± 3.7% repellant activity under laboratory conditions to 99 ± 1% in the field; DEET was 95.8% ± 4.3% under laboratory conditions and 100 ± 0% in field conditions. The evidence was graded **very low.**

One comparative study (Boonyuan 2012) did not use human volunteers; it compared varying concentrations of essential oils, including those extracted from citronella grass, and DEET in their ability to induce avoidance or escape response and mortality among *Aedes aegypti*. Mosquitoes were placed in a chamber and exposed to papers impregnated with the test substance at varying concentrations, the mosquitoes were allowed to have contact with the impregnated papers or the papers were placed in a fine mesh to avoid contact; escape response was measured by the number of knocked down/dead mosquitoes, the number of mosquitoes remaining inside the chamber, and the number that escaped to another cage. In concentrations of 2.5% and 5%, citronella had higher escape response than DEET but this was not seen at 10% concentration where DEET fared better. Mortality of mosquitoes who were allowed contact with the citronella-impregnated papers was higher than DEET at 2.5% concentration but lower than DEET at 5% and 10% concentration, among mosquitoes who were in the non-contact chamber, mortality was higher at 2.5% and 5% citronella oil concentration but was lower than DEET at 10% concentration. The evidence was graded **very low.**

Four non-comparative studies evaluated citronella oil repellent activity against mosquitoes (Nuchuchua 2009; Trongtokit 2005; Tyagi 1998; Wu 2013). One study (Nuchuchua 2009) evaluated nanoemulsions of citronella oil with or without hairy basil or vetiver oil at varied concentrations on the biting activity of *Aedes aegypti*. Mosquito repellant effect of citronella oil formulations were evaluated using a human bait technique based on the standard test of the WHO. The duration of repellency for citronella without high pressure homogenization was 1.5 +/- 0.5% while citronella with high pressure homogenization was 3.5 +/- 0.5%. The second study (Trongtokit 2005) evaluated 38 essential oils of different concentrations (undiluted, 10% and 50%) against 3 mosquito species. On 3 volunteers' forearms, extracts were applied at varying concentrations and the arms were then exposed in a cage with mosquitos for 1 minute and this was repeated every 30 minutes, The time was recorded at which the first bite was observed. Of 38 undiluted essential oils, the most effective included those extracted from *Cymbopogon nardus*; duration of repellency for the 10% dilution was 0 mins, for the 50% dilution, 50 minutes, and 120 minutes for the undiluted solution. Another study (Tyagi 1998) compared essential oils of four species and two hybrid varieties of *Cymbopogon* for their repellent properties against *Aedes aegypti, Anopheles stephensi,* and *Culex quinquefasciatus*. Repellent activity was measured in a similar way to the previously mentioned equation 100(1-t/c) % where average efficacy of the different varieties of *Cymbopogon* against *Aedes aegypti* ranged from 85%-95% and activity ranged from 1-8 hrs after application; *Cymbopogon nardus* proved to be the most

repellent essential oil at 95.7%. The fourth study (Wu 2013) evaluated the repellant activity of 11 essential oils including lemongrass & citronella oil against *Aedes albopictus*. The essential oils were used as core material while gelatin and gum arabic were used as wall materials to prepare microcapsules of essential oils which were then subjected to repellent bioassay on hand skin. A volunteer's hand dabbed with repellent was placed in a mosquito cage for 2 minutes and observations on whether the mosquitos would stop or attack were noted; once a mosquito sucked blood the repellant trial was finished and repellant effect protection time was recorded. Maximum repellency within 10 minutes for both lemongrass and citronella was 76.93 ± 3.97. The evidence was graded **very low** for the four above-mentioned studies**.**

One study (Muller 2008) evaluated citronella oil candle. Candles were lighted at varying distances from volunteers and mosquitoes landing, probing and biting on volunteer skin were counted and recorded. Repellancy rate of citronella candle at 1 meter distance = 35.4% and at 2 meter distance = 20.9%. Another study (Makhaik 2005) evaluated the insecticidal effects of citronella oil. Lethal concentration to kill 50% of *Aedes* with *Cymbopogon flexuous* was 2.65% and to kill 90% of *Aedes* was 5.32%. *Cymbopogon winterianus* performed better with lethal concentration to kill 50% *Aedes* of 5.53%. The evidence was graded **very low** for the two above-mentioned studies.

The populations studied, methodology, and outcomes monitored for the above-mentioned studies are presented in Appendix C.

There are no available data that shows direct measurement of the effectiveness of Citronella extract versus DEET in terms of reducing the incidence of Dengue. Studies showed that the protective effect of citronella varies depending on the formulation used and that lower concentrations of citronella have minimal or no repellant activity, but results were inconsistent. DEET showed higher repellency activity and had longer duration of protection. Whether reduction in biting or feeding and repellency directly measures decrease in infections caused by these mosquitoes still needs to be further evaluated.

Consideration for recommendation development during Stakeholders Panel meeting:

- There are no studies directly comparing the effectiveness of citronella compared to DEET based repellents in decreasing the incidence of dengue
- There is insufficient evidence that use of Citronella-based repellant reduces dengue transmission.
- The repellent activity of citronella varied depending on the formulation and concentration. However, because of limited studies, it is not known what would be the best formulation, preparation, and concentration of citronella for repellancy.
- The DOH representatives would rather focus on vector control and community education rather than making recommendation on using any type of insect repellant.

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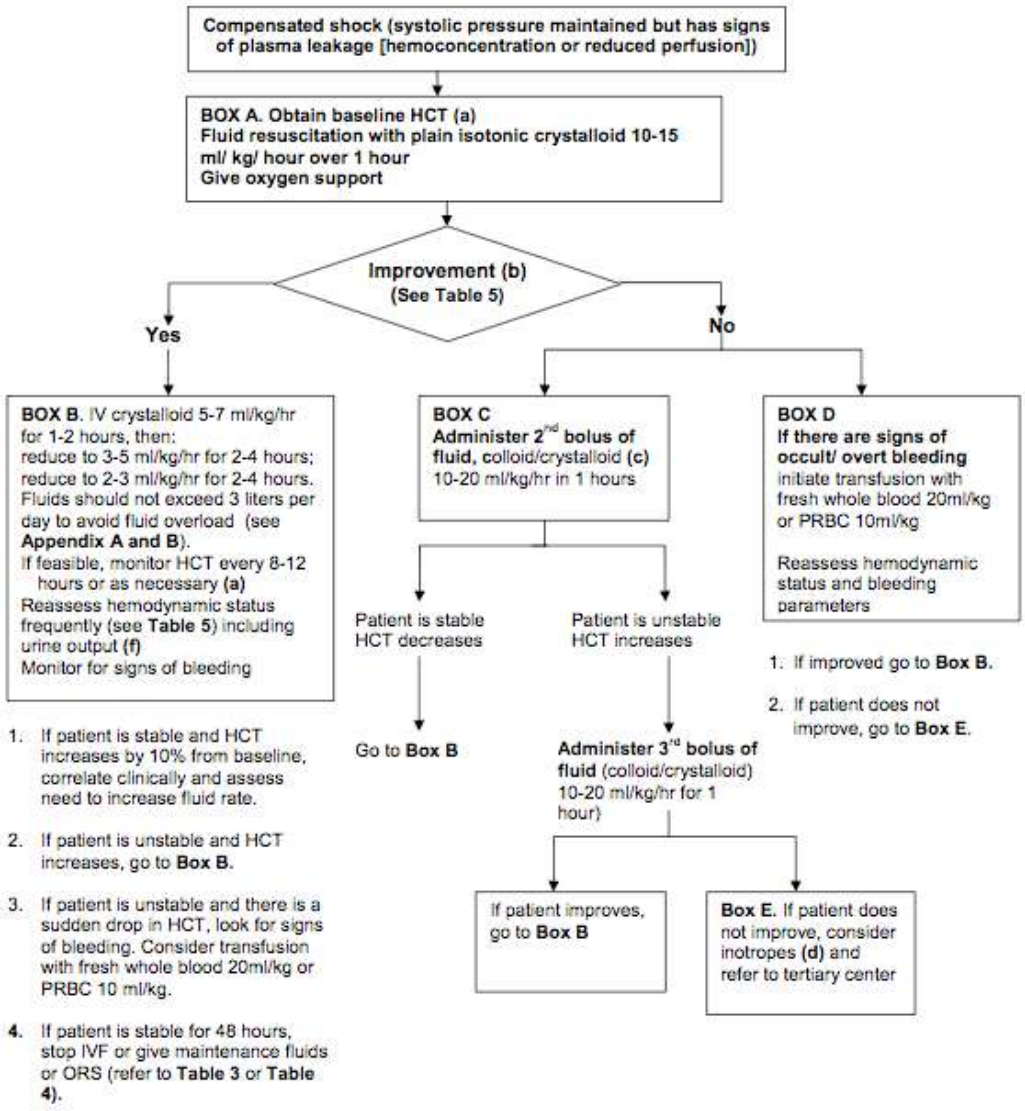
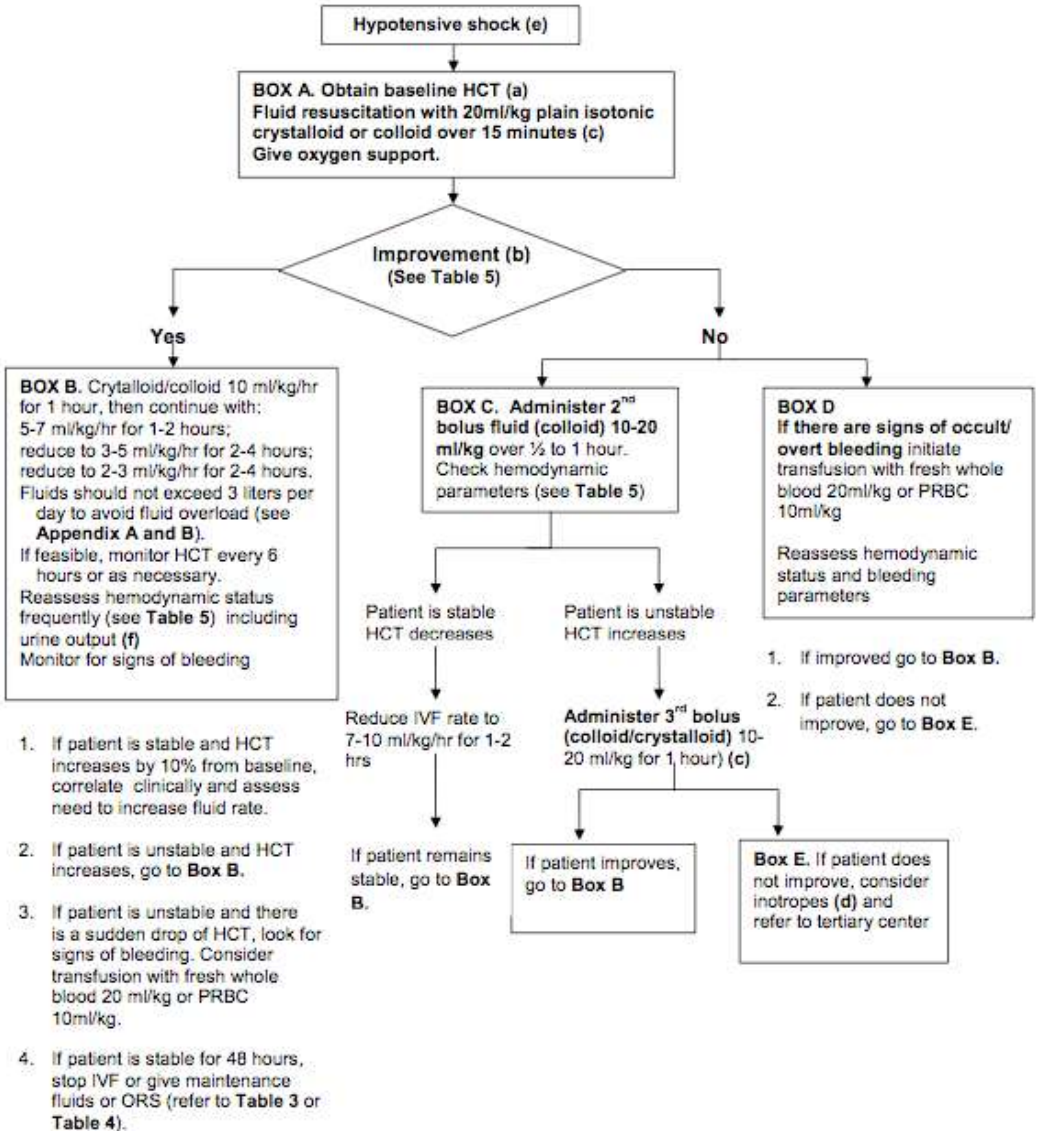
APPENDIX A

Recommendations for Fluid Therapy for Compensated Shock and Hypotensive Shock Based on the 2012 PPS Revised Guidelines on Fluid Management of Dengue Fever and Dengue Hemorrhagic Fever

A-1. Recommended Fluid Therapy for Compensated Shock



A-2. Recommended Fluid Therapy for Hypotensive Shock



APPENDIX B

Hemodynamic Assessment: Continuum of Hemodynamic Changes

Parameters	Stable Condition	Compensated Shock	Hypotensive Shock
Sensorium	Clear and lucid	Clear and lucid[a]	Change of mental state (restless, combative)
Capillary refill time	Brisk (<2 sec)	Prolonged (>2 sec)	Very prolonged, mottled skin
Extremities	Warm and pink	Cool peripheries	Cold and clammy
Peripheral pulse volume	Good volume	Weak and thready	Feeble or absent
Heart Rate	Normal for age	Tachycardia	Severe tachycardia with bradycardia in late shock
Blood pressure	Normal for age; Normal pulse pressure for age	Normal systolic pressure but rising diastolic pressure Narrowing pulse pressure Postural hypotension	Narrowed pulse pressure (<20 mmHg) Hypotension [b] Unrecordable blood pressure
Respiratory rate	Normal for age	Tachypnea	Metabolic acidosis hyperpnoea/ Kussmaul's breathing[c]

Modified from: WHO and Special Programme for Research and Training in Tropical Diseases. Dengue: guidelines for diagnosis, treatment, prevention and control -- New edition. 2009. Geneva, World Health Organization.

a - Shock can be missed if you do not touch the patient

b - Hypotension – defined as Systolic BP < 90 mm Hg or mean arterial pressure <70 mm Hg in adults or a systolic BP decrease of >40 mm Hg or < 2 SD below normal for age. In children up to 10 years old, the 5th centile for systolic BP can be determined by the formula: 70 + (age in years x 2) mmHg.

c - Gasping or apnea may also be features in hypotensive shock with cardiopulmonary failure.

APPENDIX C

SUMMARY OF EVIDENCE TABLES WITH GRADE ASSESSMENT FOR OVER-ALL QUALITY

Question 1: Among patients with confirmed or presumptive diagnosis of dengue in the outpatient setting, what clinical signs and symptoms warrant admission?

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1. Araneta AL, Arciaga RS, & Cristobal FL. Risk factors for the development of dengue shock syndrome in Zamboanga City. Western Mindanao Health Research, 2001: 3-10
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Summary of Findings Table

		Quality Assessment						Summary of Findings		
Clinical Signs/Sx	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR/HR or MD**	**Importance**
Shortness of Breath on 3rd Day	Case-control (Gibson 2013)	110 children & adolescents	Serious[5]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	OR 9.69 (1.38, 424.74)	Important

Irritability/ Drowsiness on 4th Day	Case-control (Gibson 2013)	110 children & adolescents	Serious[5]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	OR 9.93 (1.47, 69.96)	Important
Irritability/ Drowsiness on 5th Day	Case-control (Gibson 2013)	110 children & adolescents	Serious[5]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	OR 10.6 (1.08, 110.84)	Important
Pleural Effusion	Cohort (Araneta 2001,Manuel 2005, Gupta 2011)	938 hospitalized children & adolescents	Serious[1]	Not Serious	Serious[2]	Not Serious	Undetected	LOW	OR 2.11 (1.3, 3.4)	Important
Pleural Effusion	Case-control (Tantrachee-wathorn 2007)	165 hospitalized children & adolescents	Not Serious	Undetected	Serious[2]	Serious[4]	Undetected	VERY LOW	OR 7.9 (0.3, 243.5)	Important
Abdominal Pain	Cohort (Araneta 2001, Manuel 2005)	439 hospitalized children & adolescents	Serious[1]	Not Serious	Serious[2]	Not Serious	Undetected	LOW	OR 3.96 (1.24, 12.65)	Important
Abdominal Pain on 3rd Day	Case-control (Gibson 2013)	110 children & adolescents	Serious[5]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	OR 5.07 (1.51, 18.84)	Important
Abdominal Pain on 4th Day	Case-control (Gibson 2013)	110 children & adolescents	Serious[5]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	OR 6.92 (1.38, 44.38)	Important
Hepatomegaly	Cohort (Araneta 2001, Gupta 2011)	529 hospitalized children & adolescents	Serious[1]	Serious[3]	Serious[2]	Serious[4]	Undetected	VERY LOW	OR 3.13 (0.72, 13.36)	Important
Hepatomegaly	Case-control (Tantrachee-wathorn 2007)	165 hospitalized children & adolescents	Not Serious	Undetected	Serious[2]	Serious[4]	Undetected	VERY LOW	OR 1.3 (0.4, 4.2)	Important

		Quality Assessment						Summary of Findings		
Clinical Signs/Sx	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR/HR or MD**	**Importance**
Melena	Cohort (Araneta 2001, No authors listed 2005)	439 hospitalized children & adolescents	Serious[1]	Not Serious	Serious[2]	Not Serious	Undetected	LOW	OR 4.66 (1.11, 19.51)	Important
Epistaxis	Cohort (Araneta 2001, No authors listed 2005)	439 hospitalized children & adolescents	Serious[1]	Not Serious	Serious[2]	Serious[4]	Undetected	VERY LOW	OR 4.66 (0.49, 1.34)	Important
Vomiting	Cohort (Araneta 2001, No authors listed 2005)	439 hospitalized children & adolescents	Serious[1]	Serious[3]	Serious[2]	Serious[4]	Undetected	VERY LOW	OR 1.09 (0.35, 3.36)	Important
Bleeding	Cohort (Gupta 2011)	483 hospitalized children & adolescents	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	LOW	OR 1.9 (1.12, 3.15)	Important
(+) Bleeding	Case-control (Tantrachee-wathorn 2007)	165 hospitalized children & adolescents	Not Serious	Undetected	Serious[2]	Not Serious	Undetected	LOW	OR 2.7 (1.5, 17.1)	Important

		Quality Assessment						Summary of Findings		
Clinical Signs/Sx	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR/HR or MD**	**Importance**
Platelet count < 100,000/mm^3	Cohort (Araneta 2001)	46 hospitalized children & adolescents	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	LOW	OR 6.11 (1.41, 26.41)	Important
Platelet count < 50,000/mm^3	Cohort (No authors listed 2005)	393 hospitalized children & adolescents	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	LOW	OR 1.68 (1.08, 2.61)	Important
Platelet count > 20,000/mm^3	Cohort (Gupta 2011)	483 hospitalized children & adolescents	Serious[1]	Undetected	Serious[2]	Serious[4]	Undetected	VERY LOW	OR 1.3 (0.59, 2.85)	Important
Platelet count <40,000/mm^3	Cohort (Chuansumrit 2010)	101 hospitalized children & adolescents	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	LOW	RR 8.2 (1.9, 36.7)	Important
Platelet <50,000/mm^3	Case-control (Tantrachee-wathorn 2007)	165 hospitalized children & adolescents	Not Serious	Undetected	Serious[2]	Not Serious	Undetected	LOW	RR 0.2 (0.1, 0.5)	Important

		Quality Assessment						Summary of Findings		
Clinical Signs/Sx	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR/HR or MD**	**Importance**
Rise in Hematocrit >25% & Platelet <40,000	Cohort (Chuansumrit 2010)	101 hospitalized children & adolescents	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	LOW	RR 10.2 (3.3, 31.2)	Important
Rise in Hematocrit >25%	Cohort (Chuansumrit 2010)	101 hospitalized children & adolescents	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	LOW	RR 11.5 (3.3, 40.1)	Important
Hematocrit >40 vol. %	Cohort (Araneta 2001, Gupta 2011)	529 hospitalized children & adolescents	Serious[1]	Serious[3]	Serious[2]	Not Serious	Undetected	VERY LOW	OR 1.65 (1.04, 2.61)	Important
Hematocrit >50 vol. %	Cohort (No authors listed 2005)	393 hospitalized children & adolescents	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	LOW	OR 4.80 (2.26, 10.20)	Important
Hematocrit >42	Case-control (Tantrachee-wathorn 2007)	165 hospitalized children & adolescents	Not Serious	Undetected	Serious[2]	Serious[4]	Undetected	VERY LOW	OR 0.1 (0.01, 1.3)	Important

Endnotes:

1. Risk of bias inherent due to study design but in addition, all participants recruited were already the ones hospitalized and thus results may be overestimated. Sample of patients were not representative.
2. Does not directly answer the question whether these clinical signs and symptoms warrant admission, but rather whether these clinical signs and symptoms lead to dengue shock syndrome.
3. Heterogeneity is significant.
4. Confidence intervals are wide and result is inconclusive
5. Risk of bias inherent in study design and patients were not sufficiently homogenous with respect to prognostic factors. Groups that were compared were severe vs non-severe dengue.

Question 2: Among patients with dengue, which risk factors are associated with mortality?

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1. Abiera MA, Handoyo Y & Chua MN. Factors influencing mortality in DHF/DSS. Phil Journal of Pediatrics 1996; 45(2): 72-76.
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Summary of Findings Tables

		Quality Assessment						Summary of Findings		
Risk Factors	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR or MD**	**Importance**
DHF Grade III & IV	Retrospective Cohort (Fajardo 1995)	201 aged 6mos to 20yrs admitted for Dengue	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	MODERATE	OR 7.58 (2.5, 23.0)	Critical
Hypotension on Admission	Retrospective Cohort (Fajardo 1995)	201 aged 6mos to 20yrs admitted for Dengue	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	MODERATE	OR 18.27 (6.72, 49.68)	Critical
Narrow Pulse Pressure	Retrospective Cohort (Fajardo 1995)	201 aged 6mos to 20yrs admitted for Dengue	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	MODERATE	OR 3.82 (1.65, 8.88)	Critical

		Quality Assessment						Summary of Findings		
Risk Factors	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR or MD**	**Importance**
Prolonged Shock	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 191.4 (8.09, 4526.44)	Critical
Previous Dengue	Retrospective Cohort (Fajardo 1995)	201 aged 6mos to 20yrs admitted for Dengue	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	MODERATE	OR 4.74 (1.77, 12.72)	Important
Vomiting	Cross-sectional Retrospective (Mena Lora 2014)	12,321 patients with severe dengue, all ages	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Adj OR 9.8 (2.9, 33.3)	Important
Significant Bleeding	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 19.67 (1.02, 378.48)	Important
GI Bleeding	Case-control (Moraes 2013)	12,321 patients with severe dengue, all ages	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	Adj OR 2.10 (1.64, 2.69)	important
Bleeding	Prospective Cohort (Abiera 1996)	66 hospitalized children & adolescents	Serious[1]	Undetected	Not Serious	Not Estimated	Undetected	LOW	OR 7.6 (0.41, 141.31)	Important

		Quality Assessment						Summary of Findings		
Risk Factors	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR or MD**	**Importance**
Pleural Effusion	Prospective Cohort (Abiera 1996)	66 hospitalized children & adolescents	Serious[1]	Undetected	Not Serious	Not Estimated	Undetected	LOW	OR 0.11 (0.01, 1.99)	Important
Effusion	Case-control (Moraes 2013)	12,321 patients with severe dengue, all ages	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	Adj OR 2.11 (1.51, 2.96)	Important
Respiratory Failure	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 66.0 (4.57, 953.28)	Critical
Liver Failure	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 37.19 (1.9, 729.18)	Critical
Hepatic Encephalopathy.	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Serious[3]	Undetected	VERY LOW	OR 2.0 (0.19, 21.62)	Critical
Renal Failure	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 176 (9.17, 3378.87)	Critical

		Quality Assessment						Summary of Findings		
Risk Factors	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR or MD**	**Importance**
Warning Signs[4] No. 1	Case-control (Moraes 2013)	12,321 patients with severe dengue, all ages	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	Adj OR 1.00 (0.82, 1.21)	Critical
Warning Signs No. 2	Case-control (Moraes 2013)	12,321 patients with severe dengue, all ages	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	Adj OR 1.99 (1.56, 2.54)	Critical
Warning Signs No. 3	Case-control (Moraes 2013)	12,321 patients with severe dengue, all ages	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	Adj OR 4.82 (3.34, 6.96)	Critical
Warning Signs No. ≥ 4	Case-control (Moraes 2013)	12,321 patients with severe dengue, all ages	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	Adj OR 11.98 (7.60, 18.91)	Critical
Platelet Count < 30,000	Cross-sectional Retrospective (Mena Lora 2014)	796 dengue patients, all ages	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Adj OR 2.9 (1.4, 5.9)	Important
Platelet Count < 50,000-20,000	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 6.08 (1.17, 31.66)	Important

Warning signs - Severe abdominal pain, arterial hypotension, neurologic manifestation, painful hepatomegaly, hypovolemic shock, hepatic failure and myocarditis

		Quality Assessment						Summary of Findings		
Risk Factors	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR or MD**	**Importance**
Prolonged PTT	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Serious[3]	Undetected	VERY LOW	OR 14.57 (0.76, 280.39)	Not Important
Protime Prolonged 1-10sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 18%	Not Important
Protime Prolonged 11-20sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 25%	Not Important
Protime Prolonged ≥ 21sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 17%	Not Important
PTT Prolonged 11-20sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 5%	Not Important
PTT Prolonged 21-30sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 25%	Not Important

		Quality Assessment						Summary of Findings		
Risk Factors	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR or MD**	**Importance**
Platelet Nadir	Retrospective Cohort (Fajardo 1995)	201 aged 6mos to 20yrs admitted for Dengue	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	MODERATE	OR 6.95 (2.86, 16.92)	Not Important
Prolonged PTT	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Serious[3]	Undetected	VERY LOW	OR 14.57 (0.76, 280.39)	Not Important
PTT > 20 sec	Prospective Cohort (Abiera 1996)	66 hospitalized children & adolescents	Serious[1]	Undetected	Not Serious	Not Estimated	Undetected	LOW	RR 16.47	Not Important
PTT Prolonged 11-20sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 5%	Not Important
PTT Prolonged 21-30sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 25%	Not Important
PTT Prolonged ≥ 30sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 40%	Not Important

		Quality Assessment						Summary of Findings		
Risk Factors	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR or MD**	**Importance**
Protime Prolonged 1-10sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 18%	Not Important
Protime Prolonged 11-20sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 25%	Not Important
Protime Prolonged ≥ 21sec	Prospective Cohort (Chua 1993)	89 pediatric dengue patients	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Risk of Mortality 17%	Not Important
Decline in Hemoglobin	Retrospective Cohort (Fajardo 1995)	201 aged 6mos to 20yrs admitted for Dengue	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	MODERATE	OR 4.59 (1.92, 10.98)	Important
Anemia (Hgb < 9g)	Cross-sectional Retrospective (Mena Lora 2014)	12,321 patients with severe dengue, all ages	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Adj OR 3.0 (1.5, 6.1)	Important

		Quality Assessment						Summary of Findings		
Risk Factors	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR or MD**	**Importance**
Platelet count on admission <= 50,000	Retrospective Cohort (Fajardo 1995)	201 aged 6mos to 20yrs admitted for Dengue	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	MODERATE	OR 9.32 (3.43, 25.29)	Important
↑ Hct (≥ 45% for ≤ 14 yrs. old OR > 20% diff. b/win highest & lowest determinations)	Case-control (Moraes 2013)	12,321 patients with severe dengue, all ages	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	Adj OR 2.47 (1.86, 3.29)	Important
Hematocrit Increase	Retrospective Cohort (Fajardo 1995)	201 aged 6mos to 20yrs admitted for Dengue	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	MODERATE	OR 4.83 (1.92, 12.11)	Important
Mean Creatinine	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	MD -0.74 (-1.19, -2.9)	Critical
Creatinine > 1mg%	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 120 (6.21, 2319.69)	Critical

		Quality Assessment						Summary of Findings		
Risk Factors	**Study Design**	**Participants**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting Bias**	**Over-all Quality**	**OR/RR or MD**	**Importance**
Acidosis	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 15.38 (1.95, 120.98)	Critical
AST > 1000	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 18 (1.77, 183.42)	Important
Mean Albumin (g%)	Retrospective Cohort (Bunnag 2011)	59 pediatric dengue patients with shock	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	MD 1.06 (0.48, 1.64)	Not Important

Question 3: Among patients admitted because of dengue, which clinical signs and/or laboratory findings indicate significant bleeding?

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Summary of Findings Tables - Clinical Signs

Clinical Signs	Study Design	Participants	Quality Assessment					Summary of Findings		
			Risk of Bias	Inconsistency	Indirectness	Imprecision	Reporting Bias	Over-all Quality	OR/RR or MD	Importance
Abdominal Pain Before Admission	Prospective Cohort (Carlos 2005)	359 pediatric patients	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	VEY LOW	OR 1.83 (1.17, 2.88)	Important
Abdominal Pain on Admission	Prospective Cohort (Carlos 2005)	359 pediatric patients	Serious[1]	Undetected	Serious[2]	Not Serious	Undetected	VERY LOW	OR 1.83 (1.15, 2.89)	Important
Abdominal Pain	Case-control (Shivbalan 2004)	132 Indian infants & children	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	Adj OR 2.401 (0.93, 6.21)	Important
Abdominal Pain	Retrospective (Abad 1998)	145 Filipino children with DF/DHF	Very Serious[3]	Undetected	Not Serious	Not Serious	Undetected	VERY LOW	OR 3.94 (1.76, 8.80)	Important

Abdominal Pain	Prospective Cohort (Diaz-Quijano 2010)	750 children & adults	Not Serious	Undetected	Serious[4]	Not Serious	Undetected	LOW	OR 0.39 (0.24, 0.64)	Important
Pleural Effusion (UTZ)	Prospective Cohort (Abiera 1996)	66 hospitalized children & adolescents	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	RR 3.85 (1.31, 11.32)	Important
Pleural effusion (CXR)	Case-control (Shivbalan 2004)	132 Indian infants & children	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 2.48 (1.07,5.78)	Important
Serosal Effusion (ascites or pleural effusion)	Retrospective (Abad 1998)	145 Filipino children with DF/DHF	Very Serious[3]	Undetected	Not Serious	Not Serious	Undetected	VERY LOW	OR 3.86 (1.09, 13.68)	Important
Vomiting	Prospective Cohort (Diaz-Quijano 2010)	750 children & adults	Not Serious	Undetected	Serious[4]	Not Serious	Undetected	LOW	RR 1.46 (1.19, 2.96)	Important
Vomiting	Retrospective (Abad 1998)	145 Filipino children with DF/DHF	Very Serious[3]	Undetected	Not Serious	Not Serious	Undetected	VERY LOW	OR 1.31 (0.65, 2.64)	Important
Restlessness on Admission	Prospective Cohort (Carlos 2005)	359 pediatric patients	Serious[1]	Undetected	Not Serious	Serious[5]	Undetected	VERY LOW	OR 18.58 (0.99, 348.12)	Important
Rash	Prospective Cohort (Diaz-Quijano 2010)	750 children & adults	Not Serious	Undetected	Serious[4]	Not Serious	Undetected	LOW	RR 1.66 (1.25, 2.2)	Important
Hepatomegaly	Prospective Cohort (Abiera 1996)	66 hospitalized children & adolescents	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	RR 6.62 (2.15, 20.42)	Important
Hepato-splenomegaly	Retrospective (Abad 1998)	145 Filipino children with DF/DHF	Very Serious[3]	Undetected	Not Serious	Not Serious	Undetected	VERY LOW	OR 3.96(0.48,32.61)	Important

Hypotension	Retrospective (Abad 1998)	145 Filipino children with DF/DHF	Very Serious[3]	Undetected	Not Serious	Not Serious	Undetected	VERY LOW	OR 35.28 (2.1, 592.46)	Critical
Narrow Pulse Pressure	Retrospective (Abad 1998)	145 Filipino children with DF/DHF	Very Serious[3]	Undetected	Not Serious	Not Serious	Undetected	VERY LOW	OR 42.77 (2.55, 716.4)	Critical
Narrow pulse pressure	Case-control (Shivbalan 2004)	132 Indian infants & children	Serious[1]	Undetected	Not Serious	Not Serious	Undetected	LOW	OR 4.00 (1.61, 9.93)	Critical

Summary of Findings Tables - Laboratory Findings

Laboratory Findings	Study Design	Participants	Quality Assessment					Summary of Findings		
			Risk of Bias	Inconsistency	Indirectness	Imprecision	Reporting Bias	Over-all Quality	OR/RR or MD	Importance
Platelet Count < 90,000	Prospective Cohort (Diaz-Quijano 2010)	750 children & adults	Not Serious	Undetected	Serious[4]	Not Serious	Undetected	LOW	RR 1.8 (1.1, 2.94)	Important
Platelet Count < 50,000	Retrospective Cross-sectional (Rubio 2007)	215 adolescent & adult patients	Serious[1]	Undetected	Serious[4]	Not Serious	Undetected	VERY LOW	OR 77.65 (4.55, 1325.50)	Important
Platelet Count < 50,000	Case-control (Shivbalan 2004)	132 Indian infants & children	Serious[3]	Undetected	Not Serious	Not Serious	Undetected	LOW	Adj OR 4.129 (1.83, 9.314)	Important

WBC < 4,500	Prospective Cohort (Diaz-Quijano 2010)	750 children & adults	Not Serious	Undetected	Serious[4]	Not Serious	Undetected	LOW	RR 1.87 (1.19, 2.96)	Important
WBC < 5000/mm^3	Retrospective Cross-sectional (Rubio 2007)	215 adolescent & adult patients	Serious[1]	Undetected	Serious[4]	Not Serious	Undetected	VERY LOW	OR 5.23, 95% CI 1.18-23.13	Important
Prolonged PT	Prospective Cohort (Chua 1993)	89 hospitalized children & adolescents	Serious[1]	Undetected	Not Serious	Serious[5]	Undetected	VERY LOW	OR 2.70 (0.71, 10.23)	Important
PTT >30	Prospective Cohort (Chua 1993)	89 hospitalized children & adolescents	Serious[1]	Undetected	Not Serious	Serious[5]	Undetected	VERY LOW	OR 1.46 (0.24, 8.88)	Important
ALT > 3x normal value	Case-control (Shivbalan 2004)	132 Indian infants & children	Serious[3]	Undetected	Not Serious	Not Serious	Undetected	LOW	Adj OR 2.952 (1.306, 6.674)	Important

ENDNOTES:

[1] Sample of participants was not representative and there was insufficient information on whether participants were sufficiently homogenous with respect to prognostic factors

[2] Indirectness due to differences in outcome evaluated: the study did not directly determine development of bleeding but rather compared those who developed DHF with those who developed DF

[3] Sample was not representative; there was not enough information on whether participants were sufficiently homogenous with respect to prognostic factors and whether objective and unbiased outcome criteria were used. Dengue was diagnosed based on clinical criteria only and there was no laboratory confirmation of the diagnosis of dengue.

[4] Indirect because both adults and children were included

[5] Effect size is imprecise due to the wide confidence intervals; result is insignificant.

Question 4: Among Dengue patients without shock how effective are isotonic IVFs compared to hypotonic IVFs in reducing mortality?

Bibliography:
Jingjing Wang , Erdi Xu , Yanfeng Xiao. Isotonic versus hypotonic maintenance IV fluids in hospitalized children: a meta-analysis. Pediatrics 2014; 133(1): 105-113

Summary of Findings Table

№ of studies	Study design	Quality assessment					№ of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isotonic Maintenance IVFs	Hypotonic Maintenance IVFs	Relative (95% CI)	Absolute (95% CI)		
Hyponatremia												
7	RCTs	Serious[1]	not serious	Serious[2]	not serious		42/273 (15.4%)	100/281 (35.6%)	**RR 2.24** (1.52 to 3.31)	441 more than 1000 (from 185 more to 822 more)	LOW	Important
Severe Hyponatremia												
6	RCTs	Serious[1]	not serious	Serious[2]	not serious		3/214 (1.4%)	24/267 (9.0%)	**RR 5.29** (1.74 to 16.06)	386 more per 1000 (from 67 more to 1000 more)	LOW	Important

Endnotes:
1. Included studies differed in their risk of bias - three studies had unclear descriptions of their sequence generation, two studies were unclear in their allocation concealment, four of the studies used blinding methods, one study was assessed as having a high risk of incomplete outcome data.
2. Participants were hospitalized children with a mix of surgical and medical cases and NOT particularly children with dengue

Question 5: Among Dengue patients with shock, how effective are colloidal IVFs compared to crystalloid IVFs in reducing mortality?

Bibliography:

Jalac SLR, de Vera M, Alejandria MM. The use of colloids and crystalloids in pediatric dengue shock syndrome: a systematic review and meta-analysis. Philippine Journal of Microbiology and Infectious Diseases 2010; 39: 14-24.

Summary of Findings Tables

Quality assessment							Number of Patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Colloidal IVFs**	**Crystalloid IVFs**	**Relative (95% CI)**	**Absolute (95% CI)**		
Recurrence of Shock After the Initial Fluid Resuscitation												
3	randomised trials	not serious	not serious	serious [1]	serious [2]	publication bias strongly suspected [3]	34/155 (21.9%)	37/156 (23.7%)	**RR 0.92** (0.62 to 1.38)	19 fewer per 1000 (from 90 fewer to 90 more)	⊕◯◯◯ VERY LOW	Critical
Patients Who Needed Rescue Colloids After the Initial Fluid Resuscitation												
2	randomised trials	not serious	not serious	serious [4]	serious [5]	publication bias strongly suspected [3]	106/366 (29.0%)	77/239 (32.2%)	**RR 0.90** (0.70 to 1.16)	32 fewer per 1000 (from 52 more to 97 fewer)	⊕◯◯◯ VERY LOW	Important
Number of Patients Given Diuretics After Fluid Resuscitation												
2	randomised trials	not serious	not serious	serious [6]	serious [7]	publication bias strongly suspected [3]	86/366 (23.5%)	45/239 (18.8%)	**RR 1.17** (0.84 to 1.64)	32 more per 1000 (from 30 fewer to 121 more)	⊕◯◯◯ VERY LOW	Important

Total Volume of Intravenous Fluids Given												
3	randomised trials	not serious	not serious	serious [8]	serious [2]	publication bias strongly suspected [3]	385	259	-	WMD **0.8 more** (1.68 fewer to 3.28 more)	⊕◯◯◯ VERY LOW	Important
Decrease in Hematocrit (%) Levels of Patients Two Hours After Fluid Resuscitation												
3	randomised trials	not serious	serious [9]	serious [8]	not serious	publication bias strongly suspected [3]	380	262	-	WMD **7.87 fewer** (8.53 fewer to 7.22 fewer)	⊕◯◯◯ VERY LOW	Important
Decrease in Pulse Rate (Beats/Minute) of Patients Two Hours After Fluid Resuscitation												
2	randomised trials	not serious	not serious	serious [8]	not serious	publication bias strongly suspected [3]	136	136	-	WMD **3.37 fewer** (5.49 fewer to 0.8 fewer)	⊕⊕◯◯ LOW	Important

Endnotes:

1. Recurrence of shock may not always lead to mortality
2. There is a possibility of either benefit or harm as confidence interval is wide
3. Database search is limited to PubMed and Cochrane
4. The need for rescue colloids after the initial fluid resuscitation may not always lead to mortality
5. There is still a possibility of definite benefit
6. Ned for diuretics may not always lead to mortality

Question 6: Among dengue patients with no or minimal bleeding, how effective is prophylactic platelet transfusion in preventing significant bleeding and reducing mortality?

Bibliography:

1. Assir MZK, Kamran U, Ahmad HI, et al. Effectiveness of platelet transfusion in dengue fever: a randomized controlled trial. Transfus Med Hemother 2013: 40:362-368.
2. Lye DC, Lee VJ, Sun Y, Leo YS. Lack of efficacy of prophylactic platelet transfusion for severe thrombocytopenia in adults with acute uncomplicated dengue infection. Clinical Infectious Diseases 2009; 48:1262-1265.
3. Prashantha B, Varun S, Sharat D. Prophylactic platelet transfusion in stable dengue fever patients: Is it really necessary? Indian J Hematol Blood Transfus 2014; 30(2): 126-129.

Summary of Findings Tables

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considera-tions**	**Prophylactic Platelet Transfusion**	**No Platelet Transfusion**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
1	RCT	Serious [1]	Not serious	serious [2]	not serious		2/19 (10.5%)	0/20 (0.0%)	**RR 5.25** (0.27 to 102.74)	0 fewer per 1000 (from 0 fewer to 0 fewer)	MODERATE	Important
2	observational studies	Serious [3]	Not serious	serious [2]	serious [4]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [4]	1/211 (0.5%)	0/96 (0.0%)	**RR 1.10** (0.05 to 26.57)	0 fewer per 1000 (from 0 fewer to 0 fewer)	VERY LOW	Important
Bleeding												
2	observational studies	Serious [3]	Not serious	serious [2]	serious [4]	publication bias strongly suspected all plausible residual	1/211 (0.5%)	2/96 (2.1%)	**RR 0.18** (0.02 to 1.96)	17 fewer per 1000 (from 20 fewer to 20 more)	VERY LOW	Important

						confounding would reduce the demonstrated effect [4]						
Progression of Bleeding												
1	RCT	Serious	not serious	serious [2]	not serious		1/19 (5.3%)	0/20 (0.0%)	**RR 3.15** (0.14 to 72.89)	0 fewer per 1000 (from 0 fewer to 0 fewer)	MODERATE	Important
Platelet Recovery												
2	Observational studies	Serious [3]	not serious	serious [2]	serious [4]		211	96	-	Mean **0.96 more** (0.86 fewer to 2.78 more)	VERY LOW	Important
Hospital Stay in Days												
2	Observational studies	Serious [3]	not serious	serious [2]	serious [4]		211	96	-	Mean **1.19 higher** (0.71 lower to 3.08 higher)	VERY LOW	Important
Severe Anaphylaxis & Hypotension												
1	RCT	not serious	not serious	serious [2]	not serious		3/19 (15.8%)	0/20 (0.0%)	**RR 7.35** (0.40 to 133.48)	0 fewer per 1000 (from 0 fewer to 0 fewer)	MODERATE	Important

ENDNOTES:

[1] Serious bias due to unclear randomization and allocation concealment procedures. Dengue was diagnosed based on clinical criteria only and there was no laboratory confirmation of the diagnosis of dengue.

[2] Indirectness due to inclusion of only adults

[3] Observational studies with no true randomization, therefore balance between known and unknown factors is not assures. However, baseline characteristics seem comparable with known prognostic factors

[4] Imprecision due to wide confidence intervals around the point estimate that includes significant benefit and significant harm for platelet transfusion

Question 7: Among Dengue patients with significant bleeding, how effective is plasma transfusion in controlling bleeding and reducing mortality?

Bibliography:

Sellahewa KH, Samaraweera N, Thusita KPG, Fernando JL. Is fresh frozen plasma effective for thrombocytopenia in adults with dengue fever? A prospective randomized double-blind controlled study. Ceylon Medical Journal 2008; 53(2): 36-40.

Summary of Evidence Tables

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Plasma Trans-fusion**	**Isoto-nic Saline**	**Relative (95% CI)**	**Absolute (95% CI)**		
Platelet Counts at 12 Hours												
1	RCT	Not serious	Not serious	Serious [1]	Not serious	None	52	51	-	SMD **0.4 more** (0.01 fewer to 0.79 more)	MODERATE	Important
Platelet Counts at 24 Hours												
1	RCT	Not serious	Not serious	Serious [1]	Serious [2]	None	50	52	-	SMD **0.25 more** (0.14 fewer to 0.64 more)	LOW	Important
Platelet Counts at 48 Hours												
1	RCT	Not serious	Not serious	Serious [1]	Serious [2]	None	49	49	-	SMD **20.4 more** (4.89 fewer to 45.69 more)	LOW	Important

ENDNOTES:

[1] Indirectness due to inclusion of only adults, not all significant bleeding. Also subtle differences in type of population (foreign) and difference in outcome.

[2] Imprecision due to results that are not meaningful

Question 8: Among populations at risk for Dengue transmission, how effective are citronella-based repellents compared to DEET-based repellents in reducing the incidence of Dengue?

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5. Semmler M, Abdel-Gaffar F, Schmidt J, & Mehlohorn H. Evaluation of biological and chemical insect repellants and their potential adverse effects. Parasitology Research 2014; 113: 185-188.
6. Tawatsin A, Wratten SD, Scott RR, Thavara U, & Techadamrongsin Y. Repellancy of volatile oils from plants against three mosquito vectors. Journal of Vector Ecology 2001; 26(1): 76-82.
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8. Trongtokit Y, Rongsriyam Y, Komalamisra N, & Apiwathnasorn C. Comparative repellancy of 38 essential oils against mosquito bites. Phytotherapy Research 2005; 19: 303-309.
9. Tyagi BK, Shahi AK, & Kaul BL. Evaluation of repellent activities of *Cymbopogon* essential oils against mosquito vectors of malaria, filiariasis and dengue fever in India. Phytomedicine 1998; 5(4): 324-329.
10. Wu H, Fu CC, Yu CC, Feng JT, Zhang X, & Ma ZQ. Repellant activity screening of 11 kinds of essential oils against *Aedes albopictus* Skuse: microcapsule preparation of Herba Schizonepetae oil and repellent bioassay on hand skin. Transactions of the Royal Society of Tropical Medicine and Hygiene 2013; 107: 471-479.

Summary of Findings Table

Quality Assessment and Summary of Comparative Studies Evaluating Repellant Activity of citronella and DEET

Description of the Study						**Summary of Finding**		
Author	**Study Design**	**Population Studied**	**Exposures Compared**	**Methodology**	**Outcomes Monitored**	**Over-all Quality**	**Results**	**Importance**
HUMAN STUDIES								
Semmler 2014	Experimental lab testing	5 human volunteers	Extracts of *Cymbopogon nardus* and DEET	Hands of 5 volunteers covered with plastic gloves but with a circular area 4.5 cm cut out at back of the hand. 0.25 and 1% test solution applied to the naked skin and then exposed to the mosquitoes. Repellant	Biting activity of *Aedes aegypti* mosquitoes	Very Low	Biting Activity *Cymbopogon nardus* 0.25% dilution: no repellancy 1% dilution: no repellancy DEET 10% dilution: full protection within 3 minutes	**Important**

				activity was determined after 3 minutes of exposure when 3 mosquitoes have sucked blood on skin.				
Thorsell 1998	Experimental lab testing	Human volunteers	Ethanol extracts of yarrow and plant oils (eg. birch/pine tar, CITRONELLA, clove-eucalyptus, geranium, lavender, lily of the valley, and peppermint oils versus Reference repellants: DEET and DEM	1. Free surface of one hand was treated with 0.5 ml of test solution (1.2 mg/test material/cm^2) while the free surface of the other hand was untreated and served as control. Both hands were then exposed to cage where number of sucking mosquitoes was counted. The test hand was introduced inside mosquito cage after 0,4,6, and 8 hours. 2. A field test outside of the cage was carried out using the same methodology as above	Repellant activity	Very Low	Average efficacy of citronella extract with 1.2 mg/cm^2 concentration: 31.9 +/- 3.7% under lab condition and 99 +/- 1% in field condition DEET: 95.8 +/- 4.5% lab condition 100 +/- 0% field condition DEM: 100 +/- 0% lab condition 100 +/- 0% in field condition	**Important**
Tawatsin 2001	Experimental lab testing	3 human volunteers	Volatile oils extracted from 4 plants (turmeric-curcumin longa, kaffir lime, CITRONELLA GRASS and hairy basil and DEET Prepared into 2 formulations with and without vanillin	Repellancy of volatile oils was evaluated using human bait technique. Testing period lasted up to 8 hours depending on efficacy. 1. Time between application of repellants and the 2nd successive bite recorded as protection time 2, Large room evaluation: volatile oils were applied on the volunteers' legs and volunteers were placed inside a large room, exposed to mosquitoes for 10 minutes. Evaluation done by catching mosquitoes that landed on the legs	Protection time and repellancy effects	Very Low	Protection time *A. aegypti* *A. dirus* *C. quinquefasciatus* <u>Citronella without vanillin</u> 3 hrs 4 hrs 8 hrs <u>Citronella with vanillin</u> 6.5 hrs 8 hrs 8 hrs 8 hrs 6 hrs 8 hrs <u>DEET with vanillin</u> 8 hrs 8 hrs 8 hrs	**Important**
MOSQUITO STUDY								

Boonyuan 2012	Cross sectional	Mosquitoes	Varying concentrations of essential oils (2.5, 5 and 10%) extracted from hairy basil, ginger, lemongrass, citronella grass and plai and DEET	Different groups of mosquitoes were exposed to varying concentrations of essential oils and DEET. Varying levels of escape (avoidance) response in both contact and non-contact chambers were determined. Mortality of mosquitoes was observed for 30 minutes and 24 hours. The control group used a placebo.	Avoidance (escape response) and mortality	Very Low	**Citronella** **DEET** **% Avoidance** Contact 2.5% 45.4% 35.6% 5% 66.1% 36.4% 10% 3% 12.7% Non-contact 2.5% 37% 7% 5% 44.5% 14.3% 10% 4% 33.9% **LC 50 (24 hours)** Contact 2.5% 17.2% 0% 5% 6.9% 22.9% 10% 31.8% 53.3% Non-contact 2.5% 7.1% 0 % 5% 8.8% 2.1% 10% 5.8% 7.3%	

Quality Assessment and Summary of Non-comparative Studies Evaluating Repellant Activity of Citronella

Description of the Study						**Summary of Finding**		
Author	Study Design	Population Studied	Exposures Compared	Methodology	Outcomes Monitored	Over-all Quality	Results	Importance
Wu 2013	Experimental lab testing	4 human volunteers	11 essential oils including citronella oil and lemongrass oil	The various repellents tested were applied on the human volunteers' hand, the hand was placed inside the mosquito cage for 2 minutes. Observations on whether mosquitoes would stop or attack was noted. Repellent protection time was measured from the time of repellent application until the first mosquito bite.	Repellant activity against *A. albopictus*	Very Low	Maximum repellancy within 10 minutes Citironella 76.93 +/- 3.97% Lemongrass 76.93 +/- 3.97%	**Important**

Nuchuchua 2009	Experimental lab testing	3 human volunteers	Citronella oil, hairy basil oil, vetiver oil at various concentrations as nanoemulsions	Mosquito repellant effect of citronella oil formulations using human bait technique. 3 X 10 cm area on forearm of 3 volunteers marked with permanent marker and 0.1 ml of nanoemulsion applied. Forearm was exposed in a mosquito cage for 3 minutes every half hour. Nanoemulsions were prepared under 2 conditions: with and without high pressure homogenization	Biting activity of *Aedes* mosquitoes	Very Low	*Aedes* duration of repellancy Citronella without high pressure homogenization (20%) : 1.5 +/- 0.5% Citronella with high pressure homogenization: 3.5 +/- 0.5%	**Important**
Trongtokit 2005	Experimental lab testing	3 human volunteers	Biting activity of 3 mosquitoes	The extracts of 38 essential oils of different concentrations (undiluted, 10 and 50%) were applied on the volunteers' arms and exposed in a cage with mosquitoes for one minute, repeated every 30 minutes. The time was recorded at which the first bite was observed.	Repellancy of 38 essential oils	Very Low	Of 38 undiluted essential oils the most effective were extracted from *C. nardus, C. cablin, S. Aromaticum*, and *Z. limonella* which provided repellancy for 120 minutes At 10% dilution – 0 minute duration of repellancy 50% dilution – 50 minutes duration of repellancy	**Important**
Tyagi 1998	Experimental lab testing	3 human male volunteers	4 species of *Cymbopogon*	0.25ml essential oil was applied on the hand of human volunteers which was then exposed in a mosquito cage containing 20 female mosquitoes at regular intervals of 1, 4, 6 and 8 hours. Controls were carried separately with another volunteer without any essential oil. Each test and control was repeated three times. Repellent activity was determined from number of mosquitoes landing without sucking and the number of mosquitoes landing and	Antifeeding effect and repellant activity	Very Low	Average efficacy of different varieties of *Cymbopogon* essential oils against *Aedes* ranged from 85-95% Antifungal activity ranged from 1-8 hours after application	**Important**

				sucking in the experimental group compared with the control.				
Muller 2008	Experimental lab testing	6 human volunteers	5% essential oil candle of citronella, linoliol and geraniol versus Paraffin	Human volunteers had their left forearms and hands exposed in a test area. Candles were lighted at varying distance from the volunteers. Mosquitoes landing, probing and biting were counted and recorded at intervals of 5 minutes	Repellant activity	Very Low	Repellancy rate of 5% citronella candle 1 meter distance 35.4% 2 meter distance 20.9%	**Important**
Makhaik 2005	Experimental lab testing	Adult mosquitoes: *A. aegypti* and *Culex quinquefasciatus*	Essential oils from leaves of *C. winterianus* and *C. flexuous*	Mosquitoes were bred under lab conditions and placed inside test kits of each set of concentration. Solution concentrations (0.5, 1, 2, 4, 8%) were prepared by serial dilution from stock solution. Mortality of mosquitoes was recorded after 1 hour of exposure.	Lethal concentration to kill	Very Low	Lethal Concentration to kill (Mean, 95% CI (ug/L) 50% of Adult *Aedes* 95% of Adult *Aedes* *C. flexuous* 2.65% 5.32% *C. winterianus* 5.53% --	**Important**

APPENDIX D

DECLARATION OF CONFLICTS OF INTEREST

The following members of the Oversight Committee and the Guideline Writing Panel declared having interests that may be perceived as conflicts of interest:

1. Dr. J. Santos has been a resource speaker in continuing medical education activities dealing with dengue and dengue vaccines sponsored by a pharmaceutical company and is currently involved in an industry sponsored clinical trial on dengue vaccine.
2. Dr. L. Gonzales has been a resource speaker in continuing medical education activities dealing with dengue provided as an industry-sponsored CME grant hosted by PIDSP and is currently involved in an industry sponsored clinical trial on dengue vaccine.
3. Dr. R. Capeding has been a resource speaker in continuing medical education activities dealing with dengue and dengue vaccines sponsored by a pharmaceutical company and is currently involved in industry sponsored clinical trials on dengue vaccine.
4. Dr. M. Madrid is currently involved in an industry sponsored clinical trial on dengue vaccine.
5. Dr. C. Aguirre has been a resource speaker in continuing medical education activities dealing with dengue provided as an industry-sponsored CME grant hosted by PIDSP.
6. Dr. A. Bañez has been a resource speaker in continuing medical education activities dealing with dengue provided as an industry-sponsored CME grant hosted by PIDSP and on dengue vaccines sponsored by a pharmaceutical company.
7. Dr. R de Castro has been a resource speaker in continuing medical education activities dealing with dengue provided as an industry-sponsored CME grant hosted by PIDSP.
8. Dr. C. Tabora has been a resource speaker in continuing medical education activities dealing with dengue provided as an industry-sponsored CME grant hosted by PIDSP and is currently involved in an industry sponsored clinical trial on dengue vaccine.
9. Dr. A. Marasigan has been a resource speaker in continuing medical education activities dealing with dengue provided as an industry-sponsored CME grant hosted by PIDSP.
10. Dr. L. Peralta has been a resource speaker in continuing medical education activities dealing with dengue provided as an industry-sponsored CME grant hosted by PIDSP.