Pharmacotherapy for Preeclampsia in Low and Middle Income Countries: An Analysis of Essential Medicines Lists

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Abstract

Objective: To determine the prevalence of drugs for comprehensive management of preeclampsia in national essential medicine lists (EMLs) in low and middle income countries (LMICs)

Methods: We collected EMLs from the 144 LMICs identified by the World Bank through broad-based Internet searches and in collaboration with the World Health Organization. We identified therapies for hypertension, eclampsia, preeclampsia complications (e.g., pulmonary edema, thrombosis), preterm birth, and labour induction contained in the EMLs.

Results: In 91 EMLs obtained from 144 LMICs, the most commonly listed parenteral antihypertensive therapies were verapamil (63.7%), hydralazine (61.5%), sodium nitroprusside (48.3%), and propranolol (39.6%). The most prevalent oral antihypertensive therapies were nifedipine (95.6%), methyldopa (93.4%), propranolol (90.1%), and atenolol (87.9%). For eclampsia/preeclampsia, magnesium sulphate was present in 84.6% of EMLs and calcium gluconate in 85.7%. For pulmonary edema, most EMLs (94.5%) listed oral furosemide, for thrombosis 92.3% listed heparin, for acceleration of fetal pulmonary maturity 90.1% listed parenteral dexamethasone, and for labour induction 97.8% listed oxytocin or a prostanoid (usually misoprostol, 40.7%).

Conclusion: EMLs of LMICs provide comprehensive coverage of preeclampsia pharmacotherapy. These EMLs may be used as advocacy tools to ensure the availability of these therapies within each country.

Key Words: Preeclampsia, eclampsia, essential medicine list, antihypertensive agent

Competing Interests: None declared.

Received on July 27, 2012

Accepted on October 10, 2012

Résumé

Objectif : Déterminer la prévalence des médicaments permettant la prise en charge exhaustive de la prééclampsie au sein des listes de médicaments essentiels (LME) nationales des pays ne disposant que d'un revenu faible ou moyen (PRFM)

Méthodes : Nous avons regroupé les LME des 144 PRFM identifiés par la Banque mondiale par l'intermédiaire de recherches généralisées sur Internet et en collaboration avec l'Organisation mondiale de la santé. Nous avons identifié, au sein des LME, les traitements visant l'hypertension, l'éclampsie, les complications de la prééclampsie (p. ex. œdème pulmonaire, thrombose), l'accouchement préterme et le déclenchement du travail.

Résultats : Au sein des 91 LME obtenues auprès de 144 PRFM, les traitements antihypertenseurs parentéraux apparaissant le plus couramment ont été les suivants : vérapamil (63,7 %), hydralazine (61,5 %), nitroprussiate de sodium (48,3 %) et propranolol (39,6 %). Les traitements antihypertenseurs oraux les plus prévalents ont été les suivants : nifédipine (95,6 %), méthyldopa

(93,4 %), propranolol (90,1 %) et aténolol (87,9 %). Pour ce qui est de l'éclampsie / la prééclampsie, le sulfate de magnésium figurait dans 84,6 % des LME et le gluconate de calcium, dans 85,7 % de celles-ci. Pour ce qui est de l'œdème pulmonaire, le furosémide oral figurait dans la plupart des LME (94,5 %); pour ce qui est de la thrombose, l'héparine figurait dans 92,3 % des LME; pour ce qui est de l'accélération de la maturité pulmonaire fœtale, la dexaméthasone parentérale figurait dans 90,1 % des LME; et pour ce qui est du déclenchement du travail, l'oxytocine ou un prostanoïde (habituellement le misoprostol, 40,7 %) figurait dans 97,8 % des LME.

Conclusion : Les LME des PRFM offrent une couverture exhaustive de la pharmacothérapie visant la prééclampsie. Ces LME peuvent être utilisées à titre d'outils de défense des droits en vue d'assurer la disponibilité de ces traitements au sein de chaque pays.

J Obstet Gynaecol Can 2013;35(3):215–223

INTRODUCTION

The hypertensive disorders of pregnancy complicate 2% to 8% of pregnancies.[1,2] Collectively, they are responsible for up to one maternal death every seven minutes and 500 000 perinatal deaths annually, worldwide.[2,3] The most dangerous of these disorders is preeclampsia, defined as hypertension (diastolic blood pressure ≥ 90 mmHg) and proteinuria (≥ 0.3 g/24 hours) after 20 weeks' gestation.[4]

Ninety-nine percent of maternal deaths related to preeclampsia occur in low and middle income countries, where the case fatality rate is five times higher than in well-resourced countries.[2,5] The majority of these preeclampsia-related events have been attributed to delays in three aspects of care: triage, transport, and treatment.[5]

Pharmacological management of preeclampsia has five major components, depending on an individual woman's clinical presentation and the severity of her condition:

1. treatment of severe and non-severe hypertension with oral or parenteral agents;
2. magnesium sulphate for prevention or treatment of eclampsia;
3. treatment of preeclampsia-related end-organ complications, such as pulmonary edema;
4. corticosteroid therapy for acceleration of fetal pulmonary maturity in the event of iatrogenic preterm delivery for maternal and/or fetal indications; and
5. labour induction for such indicated deliveries.

Essential medicines are defined by the World Health Organization as "drugs that satisfy the health care needs of the majority of the population."[6,7] Essential medicines lists detail these essential medicines within an individual country, which may adapt the list to meet its specific needs.[8] Inclusion on an EML does not guarantee a nation's access to a medication; rather, it supports the argument that the medication should routinely be available. If it is not, the EML serves as an important advocacy tool.[9]

The United Nations Millennium Development Goal Number 5 aims to reduce maternal mortality by 75% by 2015.[10] Given the approaching deadline of this Millennium Development Goal and the important role that preeclampsia plays in maternal mortality, we sought to evaluate how the EMLs of LMICs performed in addressing the full scope of preeclampsia management.

METHODS

We identified 144 LMICs as classified by the World Bank.[11] In September 2011, the EMLs of these countries were sought through Internet searches and communication with Venture Strategies Innovations and the Maternal and Child Health Integrated Program of the United States Agency for International Development's Bureau for Global Health. First, we searched the WHO documentation page[12] and the WHO information of collections web page[13] for relevant EMLs. Second, using the Google search engine, each country's name was combined with broad search terms including "essential medicines," "essential medicine lists," "EML," and "WHO priority medicines." We accepted any EML that was published between 2000 and 2012; if more than one EML was identified for a country, the most recently published was used.

Each of the identified EMLs was evaluated according to its inclusion of medications important for each aspect of preeclampsia care:

1. Oral and parenteral antihypertensive therapy for non-severe and severe hypertension, including alpha blockers, cardio-selective and non-selective beta blockers, direct-acting vasodilators, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and diuretics;
2. magnesium sulphate (and its antidote, calcium gluconate) for prevention and treatment of eclampsia;

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ARB	angiotensin II receptor blocker
BP	blood pressure
EML	essential medicines list
LMICs	low and middle income countries

Geographical and income distribution of identified EMLs in 144 LMICs		
	EMLs (n = 91) n (%)	No EMLs (n = 53) n (%)
Geographic distribution		
East Asia and Pacific	14 (15.4)	10 (18.9)
Eastern Europe and Central Asia	9 (9.9)	13 (24.5)
South Asia	8 (8.8)	0 (0)
Latin America and the Caribbean	18 (19.8)	12 (22.6)
Middle East and North Africa	11 (12.1)	2 (3.8)
Sub-Saharan Africa	31 (34.1)	16 (30.2)
Income level		
Low	28 (30.8)	12 (22.6)
Low-middle	42 (46.2)	14 (26.4)
Middle	21 (23.1)	27 (50.9)

3. treatment of preeclampsia-related complications of pulmonary edema with diuretics or thromboembolism with heparin;

4. parenteral betamethasone or dexamethasone for acceleration of fetal pulmonary maturity in the face of iatrogenic preterm birth at < 34 weeks; and

5. labour induction with prostanoids and/or oxytocin for indicated delivery.

Within each of the five aspects of preeclampsia care, we evaluated the number and proportion of EMLs that listed each medication relevant to an aspect of care, and noted both dosage and route of administration. We did so for completeness and because medications that are not in common use may be effective and acceptable for a given indication in pregnancy (e.g., propranolol for hypertension). Graphical display and discussion are presented only for those medications listed by at least 20% of EMLs.

RESULTS

The World Bank identified 144 LMICs, and we identified EMLs for 91 of these (63.2%). Thirty-one percent of the EMLs were from low income countries, 46% from low-middle income countries, and 23% from high-middle income countries. Of the 53 EMLs not collected, 23% were from low income, 26% from low-middle income, and 51% from high-middle income countries. A list of these LMICs with links to their EMLs, in addition to a list of countries without identifiable EMLs, is given in the online eAppendix. The majority of the 91 identified EMLs (92.3%) had been updated since 2005.

The EMLs collected were distributed across the six regions categorized by the World Bank, as shown in the Table.[11] One third of the EMLs collected (34.1%) were in Sub-Saharan Africa, and the smallest number of EMLs collected (8.8%) were in South Asia. EMLs not collected were distributed evenly across four regions; South Asia had no missing EMLs, and Middle East and North Africa had only 3.8% of EMLs absent.

Parenteral antihypertensive therapy for severe hypertension was widely cited by the identified EMLs; 84 (92.3%) listed at least one parenteral agent to treat severe hypertension. The most common parenteral agent listed was verapamil, followed by hydralazine, sodium nitroprusside, and propranolol (Figure 1). Parenteral labetalol, used commonly for severe hypertension in well-resourced settings, was listed by only 19.8% of EMLs (not shown in Figure 1). A complete account of listed parenteral agents is shown in Figures 2 to 4).

The wide listing of oral antihypertensive therapy for severe or non-severe hypertension is shown in Figures 5 to 7. Most EMLs list methyldopa (a centrally acting alpha receptor blocker), atenolol (cardioselective beta blocker), or propranolol (non-selective beta blocker) (Figure 5). Both carvedilol and labetalol are oral alpha- and non-specific beta blockers, although oral labetalol was listed less commonly, by 12.1% of EMLs (not shown in Figure 5). Nifedipine is the most widely listed direct-acting vasodilator, cited by almost all EMLs (Figure 6). An individual EML may have more than one preparation of a drug listed; the 207 nifedipine preparations listed consisted of 5 mg capsules (n = 10), 10 mg capsules or tablets (n = 73), 20 mg tablets (intermediate or slow release) (n = 59), 30 to 90 mg extended release (n = 40), and dose unspecified (n = 7). Approximately two

Figure 1. Parenteral antihypertensive agents

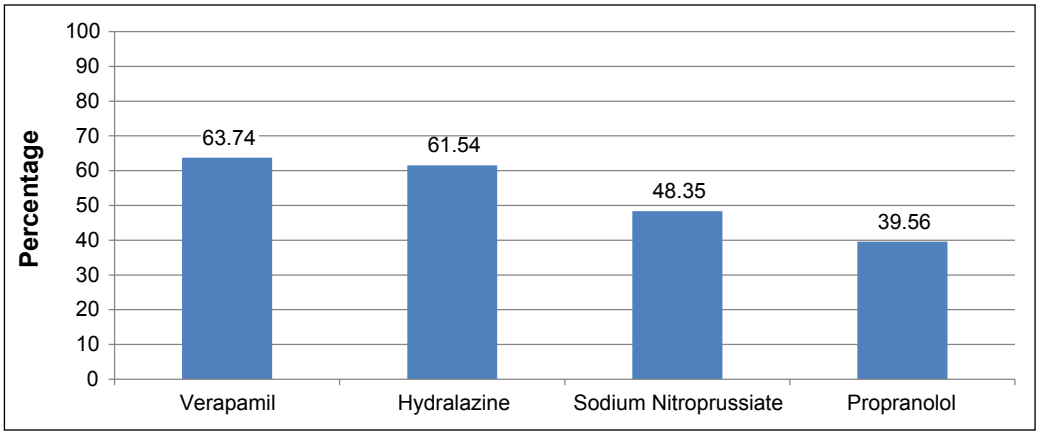


Figure 2. Parenteral alpha agonist and beta-blocker antihypertensive agents

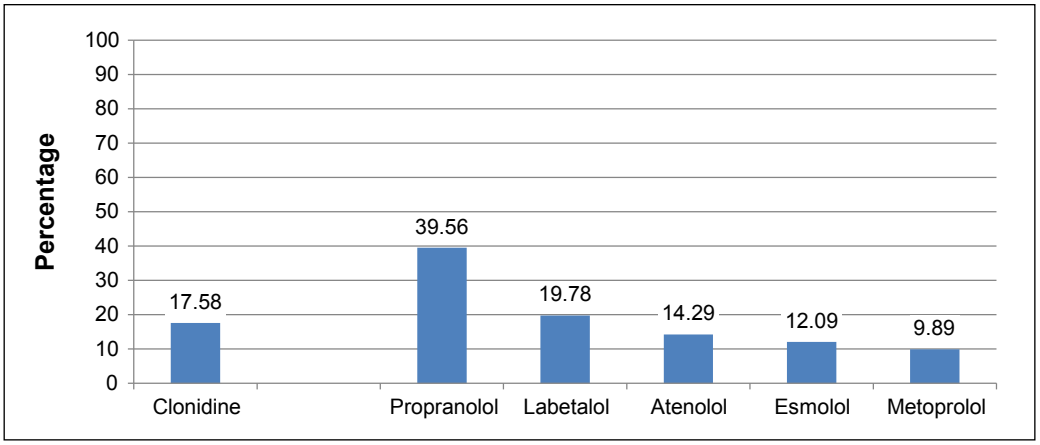


Figure 3. Parenteral direct-acting vasodilators

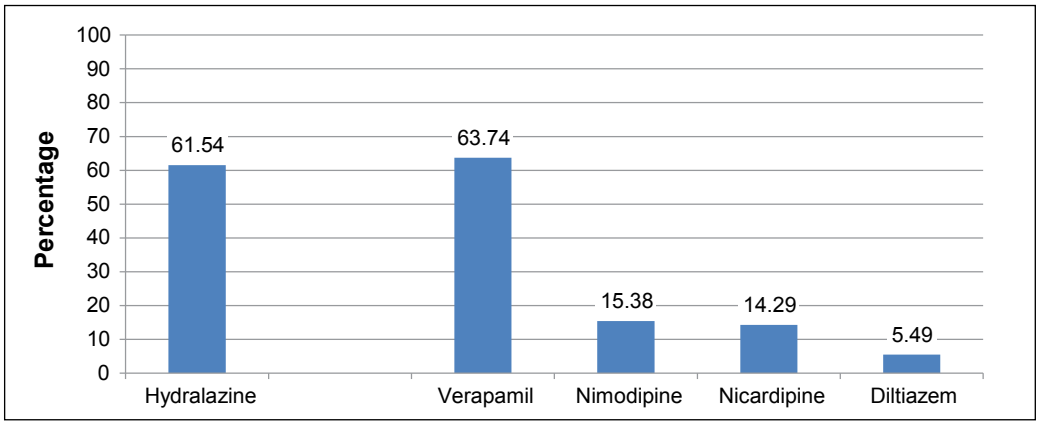


Figure 4. Parenteral ACE inhibitors or ARBs

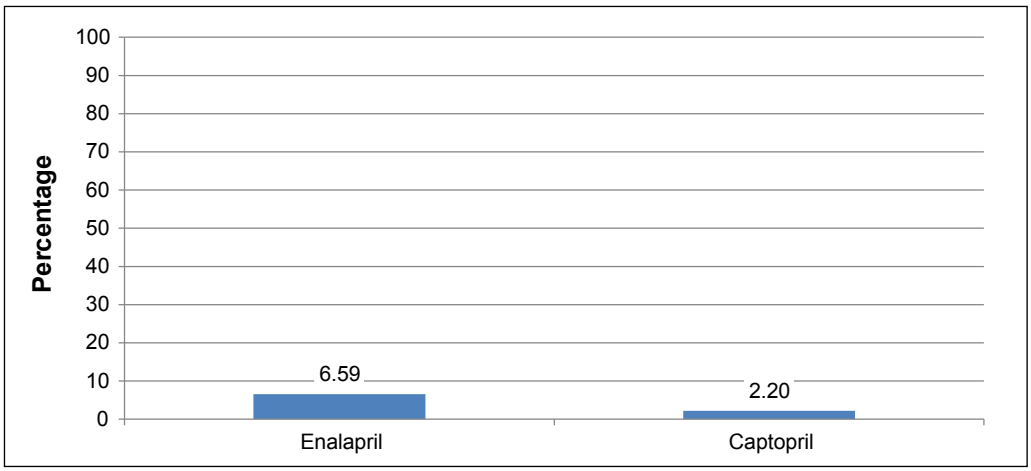


Figure 5. Oral alpha- and/or beta-blocking antihypertensive agents

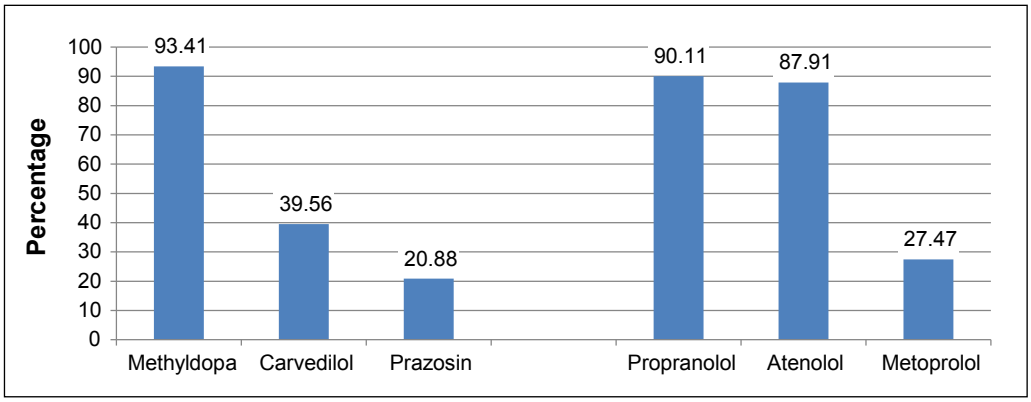


Figure 6. Oral direct-acting vasodilators

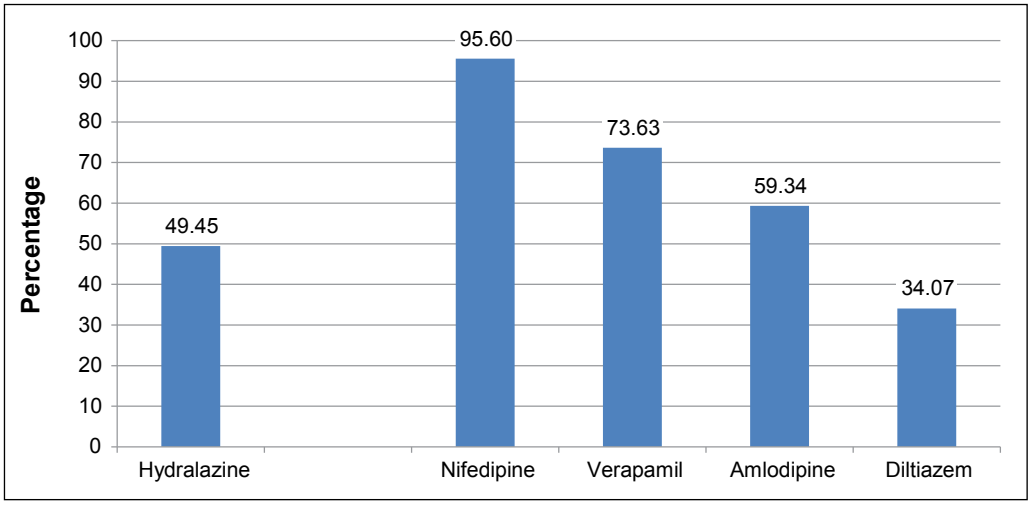
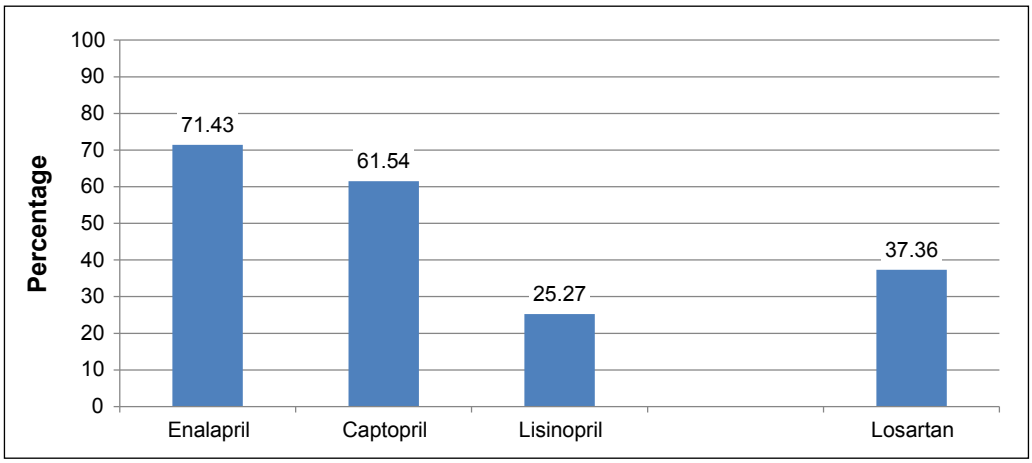


Figure 7. Oral ACE inhibitors or ARBs



thirds of EMLs list ACE inhibitors or ARBs, particularly captopril or enalapril (Figure 7). Hydrochlorothiazide (82 EMLs, 90.1%) and spironolactone (83 EMLs, 91.2%) are also widely listed in EMLs (not shown).

For prevention and treatment of eclampsia, 84.6% of EMLs listed magnesium sulphate, and 85.7% listed calcium gluconate. The concentrations of magnesium sulphate available varied from 0.15 mg/mL (1.1%) to 500 mg/mL (53.8%); this excludes continuous intravenous dosing, 10 g injections and powder formulations. Although a wide range of dosages were present in EMLs, the majority listed the 500 mg/mL formulation of magnesium sulphate.

For treatment of pulmonary edema, a complication of preeclampsia, furosemide was listed by most EMLs (94.5% for the oral preparation and 92.3% for parenteral). For treatment of thrombosis, heparin injections with dosages ranging from 100 IU to 25 000 IU were present in 92.3% of EMLs, including various doses of unfractionated and low molecular weight heparin. For acceleration of fetal pulmonary maturity, 90.1% of EMLs listed parenteral dexamethasone but only 19.8% listed parenteral betamethasone.

For labour induction, oxytocin is almost uniformly listed on EMLs (97.8%). Prostanoids are less widely cited, as follows: 40.7% oral misoprostol, 3.3% oral dinoprostone, 1.1% oral prostaglandin, 14.3% parenteral prostaglandin, 7.7% parenteral dinoprostone, 13.2% vaginal dinoprostone, 3.3% prostaglandin gel or powder, and 1.1% vaginal prostaglandin.

DISCUSSION

National EMLs are critical for dialogue aimed at improving pregnancy care in LMICs. As far as we are aware, our study is the first to examine how well the national EMLs of LMICs address the spectrum of pharmacotherapy for preeclampsia. Upon review of the 91 available EMLs covering a large number of geographical locations (63.2% of the 144 LMICs identified by the World Bank), our findings indicate that national EMLs contain medications for comprehensive coverage of all aspects of recommended preeclampsia pharmacotherapy. Most (> 80%) of the identified EMLs listed at least one effective parenteral antihypertensive agent (usually hydralazine or verapamil), at least one effective oral antihypertensive agent (usually nifedipine or methyldopa), magnesium sulphate (and its antidote, calcium gluconate), furosemide, heparin, a parenteral corticosteroid, and agents for labour induction (oxytocin and, less frequently, a prostanoid).

The identified EMLs represent all regions categorized by the World Bank. Of the 10 countries that represent 60% of maternal mortality (i.e., India, Nigeria, Democratic Republic of the Congo, Sudan, Pakistan, Indonesia, Ethiopia, Tanzania, Bangladesh, and Afghanistan), all had accessible EMLs, all of which were included in our study.[5,14] The great majority of LMICs in South Asia, the Middle East, and North Africa had identifiable EMLs. Most countries in Eastern Europe and Central Asia did not have identifiable EMLs.

Following publication of the landmark Eclampsia Trial in 1995,[15] reports of essential medicines for preeclampsia focussed on the presence of magnesium sulphate on EMLs.[16] By 2005, most EMLs surveyed listed magnesium sulphate,[17,18] and our study confirmed that this is still the case.

More limited data exist on EMLs and their inclusion of antihypertensive agents. A study in sub-Saharan Africa

showed a strong presence of oral antihypertensive agents in EMLs, such as hydrochlorothiazide (85%), atenolol (77%), propranolol (92%), and nifedipine (85%),[19] similar to our analysis (90.1%, 87.9%, 90.1%, and 95.6%, respectively).

There are many acceptable choices of parenteral antihypertensive agents for treatment of severe hypertension, and most EMLs have at least one appropriate agent. Severe hypertension, defined as a systolic blood pressure ≥ 160 mmHg and/or a diastolic BP ≥ 110 mmHg, is the only modifiable complication of preeclampsia. It is widely accepted that women with severe hypertension are at increased risk of stroke and will therefore benefit from BP reduction. The most commonly recommended agents are parenteral labetalol or hydralazine,[20,21] or sublingual nifedipine, oral immediate-acting nifedipine or oral intermediate-acting nifedipine.[20,22,23] We have learned from the United Kingdom's Confidential Enquiry into Maternal and Child Health that failure of effective antihypertensive therapy for severe hypertension is the most common source of sub-standard care of women with preeclampsia, even in well-resourced settings.[24] Relevant systematic reviews have failed to show clear differences between parenteral antihypertensive agents that would favour one over others. Only ACE inhibitors and ARBs are contraindicated for use antenatally, although captopril, enalapril, and quinapril are acceptable for use by breastfeeding mothers.

There are also many reasonable choices for oral antihypertensive therapy, usually for non-severe hypertension, and virtually all EMLs list at least one oral agent. Although the most commonly recommended agents in pregnancy are oral methyldopa, labetalol, beta blockers, and calcium channel blockers,[25] relevant systematic reviews indicate neither clear benefits of treatment nor clear differences between one agent or another.[22] What has been shown is that treatment of non-severe hypertension will decrease the incidence of BP values of ≥ 160/100 mmHg later in pregnancy.[22]

Life-saving medications from EMLs have been condensed to form the *Priority Medicines for Mothers and Children* released by the WHO in 2011.[26] This document did not address the treatment of severe hypertension, although we have successfully advocated for the addition of an antihypertensive agent for the 2012 version. Similarly, no antihypertensive agent was included in the medication list of the 2012 United Nations Commission on Life-Saving Commodities for Women and Children, which advocated for the use of magnesium sulphate to lower BP. This is not recommended based on the results of trials.[27] Although observational studies suggest that there may be some transient lowering of BP 30 minutes after administration of 2 to 5 g of IV magnesium sulphate, usually in patients with preeclampsia, a sustained antihypertensive effect cannot be anticipated.[28–31] The majority of these women (approximately 75%) will require antihypertensive therapy even while on magnesium sulphate and approximately 50% will require rapid-acting medication to lower BP acutely.[5,16]

There is a lack of data with respect to the listing of labour induction therapies in EMLs. On the basis of existing evidence, it would seem appropriate that oral misoprostol is the most commonly listed prostanoid on EMLs. The WHO labour induction guidelines recommend oral misoprostol before vaginal misoprostol; however, if neither is available, the use of oxytocin is recommended.[32] This is supported by a systematic review of relevant trials which has shown that oral misoprostol is more effective than vaginal dinoprostone in decreasing the rate of Caesarean section (21% vs. 26%; RR 0.87, 95% CI 0.77 to 0.98).[33] Vaginal prostaglandins have also been found to be effective, although the best vehicle for delivering the prostaglandin is still unclear.[34] This is mirrored in the EMLs because various preparations are listed.

A strength of our study is the comprehensive review of the full spectrum of preeclampsia pharmacotherapy. A limitation of our study is that we were able to identify only 63% of national EMLs from LMICs. We attempted to review the most recent EMLs, but it is possible that a more current version was not available to us. While our study highlights the importance of recognizing the different components of preeclampsia management, listing of a medication on an EML does not guarantee the availability of that medication in the country's hospitals, nor does it even indicate that it is available in that country at all. Barriers to availability are complex and require discussion at the user, service delivery, and global levels. At the user level, barriers include high cost of essential commodities, lack of awareness of how, why, and when to use these commodities, exclusion of these commodities for some groups (e.g., lack of formulations safe for children), and limited service choices. At the service delivery level, barriers include inadequate funding, inadequate regulatory capacity at the national level to protect people from substandard or counterfeit products that can cause harm, weak supply chains, inadequately trained or underpaid service providers, and absence of comprehensive one-stop quality care facilities. At the global level, barriers include gender inequality, infringement of human rights, politicization of sexual and reproductive health, and financial constraints.[17,35–37] However, the presence of a medication on an EML may assist those who advocate for the availability of appropriate medications and high-quality care.[9]

CONCLUSION

Review of available EMLs from LMICs indicates the potential for the provision of comprehensive preeclampsia care, including treatment of severe and non-severe hypertension, eclampsia treatment and prevention, and indicated delivery of preterm and term gestations. These EMLs are fundamental to providing a rationale for governing bodies to supply these medicines to their respective populations to allow them to achieve the highest attainable standard of health. EMLs provide a source of information to allow transparency in the pharmaceutical sector. Barriers to the availability of essential medicines such as cost, lack of knowledge, weak supply chains, and inadequately trained service providers can be managed by increasing awareness and knowledge and by prioritizing the national supply of these medicines. It is important to address both the reasons that EMLs are not easily accessible for more LMICs and the problems with supply and distribution of generic essential medicines to rural service facilities.

ACKNOWLEDGEMENTS

This work is part of the University of British Columbia PRE-EMPT (Pre-eclampsia/Eclampsia, Monitoring, Prevention and Treatment) initiative supported by the Bill & Melinda Gates Foundation.

Ms Lalani is supported by the University of British Columbia Summer Student Research Program. Dr Firoz is supported by the Clinician Investigator Program, University of British Columbia. Dr Magee is supported by the Children's and Women's Health Centre of British Columbia. Dr von Dadelszen is supported by the Michael Smith Foundation and Child & Family Research Institute.

We would like to acknowledge Richard Lowe from Venture Strategies Innovations and USAID's Maternal and Child Health Integrated Program for their assistance in acquiring updated Essential Medicine Lists.

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