GUIDELINES FOR THE PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV) DO NOT ADDRESS ECONOMIC VARIATION, AFFORDABILITY IN DIFFERENT POPULATIONS, AND DRUG AVAILABILITY

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Abstract

•Introduction: Several organizations have published effective guidelines for CINV. Evidence –based guidelines list the best known regimens for prevention of CINV in different emetic risk groups. While useful, this approach may not address economic realities of availability and affordability of antiemetics in most countries and for most patients.

•Objectives: Establish a framework addressing affordability of CINV regimens in different economic settings to indicate guidance for improving antiemetic control.

•Methods: We examined current guideline recommendations in 5 CINV risk categories (from high to minimal risk), and as a consensus group listed regimens for each setting as a Good regimen, a Better regimen, or Best regimen. The World Bank / WHO established four economic groups into which each nation is placed. Additionally, the WHO approached healthcare affordability based on income levels per country (especially minimum wage). Acquisition price and availability of recommended antiemetics in each country was determined.

•Results. The greatest economic issues were seen in the two top emetic risk groups, where NK1-based regimens were often not affordable except in the highest income nation group (but not in all these countries). Widespread availability of generic agents has improved affordability. Two-agent regimens were affordable in most economic groups, as were olanzapine-based three agent regimens. Differences still existed among countries of the same economic group.

•Conclusions. The Best antiemetic regimen should always be used where it is available and affordable. Where economic realities exist limiting Best regimen use, Good and Better regimens provide realistic CINV prevention for many nations. This model may be useful in other oncology settings.

Antiemetic Guidelines

Multiple National and International Antiemetic Guidelines have been published and are widely used. Among the more popular guidelines are:

- ASCO
- MASCC / ESMO
- NCCN

Evidence affects all guidelines, but some are more evidence-based while others center their recommendations on the consensus of the group. There are advantages to each approach:

- While evidence-based guidelines are the most desirable, the problem continues that high quality evidence is not available for all clinical settings
- Consensus centered guidelines have the advantage of addressing many clinical settings; however, if the guidance is not correct due to lack of evidence, users may lose confidence in the guideline

Several studies have indicated that better outcomes result from the use of major guidelines, such as those listed above. While this is highly desirable, for the most part, guidelines do not include economic, affordability or availability issues. These issues affect the majority of people with cancer worldwide. For the most part, guidelines are developed in and for the wealthiest nations. This issue affects nearly all guidelines, not just those dealing with nausea and vomiting.

The current project was initiated to examine these economic and availability issues and to suggest an approach of making guidelines more appropriate internationally.

Objectives

•Review current Antiemetic Guidelines and create a consensus average representative antiemetic dosing regimen for one cycle.

• Determine availability and affordability of medications in different countries including examples from all World Bank Income Group.

• Establish a framework addressing affordability of Antiemetic regimens in different economic settings to indicate guidance for overcoming or approaching these guideline issues to improve control of emesis in most countries.

Table 1.Recent Antiemetic Guidelines

The latest recommendations for antiemetic prophylaxis				
Emetic risk:	Administration	MASCC/ESMO	ASCO	NCCN
HEC – cisplatin	Day 1	5HT ₃ RA + DEX + NK ₁ RA or 5HT ₃ RA + DEX + OLA or 5HT ₃ RA + DEX + NK ₁ RA + OLA	5HT ₃ RA + DEX + NK ₁ RA or + NK ₁ RA + OLA	5HT ₃ RA + DEX + NK ₁ RA or 5HT ₃ RA + DEX + OLA or 5HT ₃ RA + DEX + NK ₁ RA + OLA
	Days 2-4	DEX ¹ or DEX + OLA	DEX + OLA	DEX ¹ or OLA or DEX + OLA
HEC – AC	Day 1	5HT ₃ RA + DEX + NK ₁ RA or 5HT ₃ RA + DEX + OLA or 5HT ₃ RA + DEX + NK ₁ RA + OLA	5HT ₃ RA + DEX + NK ₁ RA or + NK ₁ RA + OLA	5HT ₃ RA + DEX + NK ₁ RA or 5HT ₃ RA + DEX + OLA or 5HT ₃ RA + DEX + NK ₁ RA + OLA
	Days 2-4	None ¹ or OLA	OLA	DEX ¹ or OLA or DEX + OLA
MEC	Day 1	5HT ₃ RA + DEX + NK ₁ RA	5HT ₃ RA + DEX + NK ₁ RA	5HT ₃ RA + DEX + NK ₁ RA or 5HT ₃ RA + DEX + OLA or 5HT ₃ RA + DEX + NK ₁ RA + OLA
	Days 2-3	None ¹	None	DEX ¹ or OLA or DEX + OLA
	Day 1	5HT ₃ RA + DEX	5HT ₃ RA + DEX	5HT ₃ RA + DEX or 5HT ₃ RA + DEX + NK ₁ RA or 5HT ₃ RA + DEX + OLA
	Days 2-3	DEX or none	DEX or none	DEX ¹ or 5HT ₃ RA or OLA
Other	Day 1	5HT ₃ RA + DEX	5HT ₃ RA + DEX	5HT ₃ RA + DEX or 5HT ₃ RA + DEX + NK ₁ RA or 5HT ₃ RA + DEX + OLA
	Days 2-3	None	None	DEX ¹ or 5HT ₃ RA or OLA
IEC	Day 1	5HT ₃ RA or DEX or DOPRA	5HT ₃ RA or DEX	5HT ₃ RA or DEX or DOPRA
	Days 2-3	None	None	None
MEC	All days	No routine antiemetics	No routine antiemetics	No routine antiemetics

A, anthracycline; AUC, area under the concentration curve; C, cyclophosphamide; DEX, dexamethasone; DOPRA, dopamine-receptor antagonist; HEC, high emetic risk chemotherapy; IEC, low emetic risk chemotherapy; MEC, moderate emetic risk chemotherapy; MEIC, minimal emetic risk chemotherapy; OLA, olanzapine.

Table 2. MASCC-ESMO Consensus Representative Antiemetic Dosing Regimens

Medication	Dose (PO) for Acute CINV
Ondansetron	8 mg
Dexamethasone	12mg
Aprepitant	125 mg on day of therapy, 80 mg daily for 2 days after
Olanzapine	10 mg daily for 4 days

Figure 1. World Bank Income Groups

Gross National Income (GNI) is defined as the total domestic and foreign output claimed by residents of a country, consisting of gross domestic product (GDP), plus factor incomes earned by foreign residents, minus income earned in the domestic economy by nonresidents.

GNI = GDP + Money flowing from foreign countries – Money flowing to foreign countries

A country's GNI in local (national) currency is converted into U.S. dollars using the Atlas conversion factor (three-year average of exchange rates, adjusted for inflation). Resulting GNI in U.S. dollars is divided by the country's midyear population to obtain the GNI per capita

Low-income (dark blue) – GNI per capita of \$1,005 or less in 2016

Lower middle-income (light blue) - GNI per capita between \$1,006- \$3,955

Upper middle-income (pink) - GNI per capita between \$3,956 - \$12,235

High-income economies (red) - GNI per capita of \$12,236 or more.

Table 3. GNI per capita in selected countries

Country by Economic Tier	Annually	Monthly	Daily
LOW:			
Ethiopia	\$660	\$55	\$1.83
Nepal	\$730	\$61	\$2.00
LOW MIDDLE:			
Honduras	\$2150	\$179	\$5.97
Pakistan	\$1500	\$125	\$4.16
Indonesia	\$3400	\$283	\$9.44
UPPER MIDDLE:			
Iran	\$5470	\$456	\$15.20
Belarus	\$5600	\$467	\$12.00
UPPER:			
USA	\$56,850	\$4,738	\$157.91
Canada	\$48,910	\$4,075	\$134
UK	\$42,370	\$3,531	\$117.69

Availability and Affordability

• One third of the global population lacks reliable access to needed medicines.

• The situation is even worse in the poorest countries where 50% or more of the population lacks such access.

• There are many ways to calculate affordability relating the cost of treatment to individuals' income. The WHO utilizes the daily wage of the lowest-paid unskilled national government worker for comparison with the cost of a defined course of treatment for a specific condition. Other methods could use relationship to average wages.

Table 4. Minimum Wage per Country per Year and Daily in US dollars

Country by Economic Tier	Minimum wage per year	Minimum wage per day
LOW:		
Ethiopia	\$216	\$0.59
Nepal	\$933	\$2.56
LOW MIDDLE:		
Honduras	\$2,892	\$8
Pakistan	\$1,800	\$4.93
UPPER MIDDLE:		
Iran	\$2,580	\$7.06
Belarus	\$1,368	\$3.75
UPPER:		
USA	\$15,080	\$41
Canada	\$18,022	\$49
UK	\$20,687	\$46

Good, Better, Best

- We proposed "Good, Better, and Best" Antiemetic regimens based on availability, and viewed by affordability in economic groups (Table 5), for Highly Emetic Settings.

-The "Best" regimen for high risk emesis is not available in all countries (generally, lack of NK1 Receptor Antagonists (Nepal, Ethiopia and Indonesia).

-The "Better" regimen is available in all economic areas, in all countries we queried (Fig 2 & 3).

- A guiding principle is that the most effective regimen must be given when affordable

Figure 2. Cost of 1 Cycle for High Emetic Risk by Economic Region

Figure 3. Days Worked for 1 Antiemetic Cycle (Based on GNI Average Daily Income)

Table 5. Good, Better, Best approach for Antiemetic Therapy

	Medications	Applies to:	Typical Acquisition Price by Economic Region
Good	Ondansetron + Dexamethasone	Some Moderate and Low Emetic Risk)	Low - \$0.45 Low Middle - \$0.76 Upper Middle - \$0.26 Upper - \$1.31
			Low - \$0.85 Low Middle - \$1.36 Upper Middle - \$1.71 Upper - \$9.31
Better	Ondansetron + Dexamethasone + Olanzapine	Some Moderate Emetic Risk High Emetic Risk (in some countries)	Low - \$0.85 Low Middle - \$1.36 Upper Middle - \$1.71 Upper - \$9.31
Best	Aprepitant + Ondansetron + Dexamethasone + Olanzapine	High Emetic Risk High-Moderate Risk	Low – Not available Low Middle - \$14.16 Upper Middle - \$16.23 Upper-- \$280.47

Results

• "Best" or "Better" Regimens appear to be available in all economic regions.

• When the "Good, Better, Best" approach is used, about the same number of days worked for acquisition of antiemetic regimen applies in each region,

• While the concept of days worked to afford a treatment is a reasonable first approach, it does not take into account other medical costs, other daily expenses, and reserve funds that differ greatly by family and economic region

• Pakistan provides a good example of availability with greatly differing affordability by regimen

Conclusions

• Guidelines meant to be used internationally should encompass economic realities

• The "Good, Better, Best" concept is an approach that illustrates a way to do this

• The costs are based on pharmacy acquisition costs, and not on retail prices which may vary and affect affordability. Additionally, while agents may be legally available in a country, they may not be found at all pharmacies or clinics.

• The most effective regimen must be given when affordable and available

• This model may be useful in other oncology settings.

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