

# Guidelines for the Management of Extremely Premature Deliveries: A Systematic Review

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abstract

**BACKGROUND AND OBJECTIVES:** Available data on survival rates and outcomes of extremely low gestational age (GA) infants (22–25 weeks' gestation) display wide variation by country. Whether similar variation is found in statements by national professional bodies is unknown. The objectives were to perform a systematic review of management from scientific and professional organizations for delivery room care of extremely low GA infants.

**METHODS:** We searched Embase, PubMed, and Google Scholar for management guidelines on perinatal care. Countries were included if rated by the United Nations Development Programme's Human Development Index as "very highly developed." The primary outcome was rating of recommendations from "comfort care" to "active care." Secondary outcomes were specifying country-specific survival and considering potential for 3 biases: limitations of GA assessment; bias from different definitions of stillbirths and live births; and bias from the use of different denominators to calculate survival.

**RESULTS:** Of 47 highly developed countries, 34 guidelines from 23 countries and 4 international groups were identified. Of these, 3 did not state management recommendations. Of the remaining 31 guidelines, 21 (68%) supported comfort care at 22 weeks' gestation, and 20 (65%) supported active care at 25 weeks' gestation. Between 23 and 24 weeks' gestation, much greater variation was seen. Seventeen guidelines cited national survival rates. Few guidelines discussed potential biases: limitations in GA ( $n = 17$ ); definition bias ( $n = 3$ ); and denominator bias ( $n = 7$ ).

**CONCLUSIONS:** Although there is a wide variation in recommendations (especially between 23 and 24 weeks' GA), there is general agreement for comfort care at 22 weeks' GA and active care at 25 weeks' GA.

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Since the advent of modern intensive care for the premature infant, a steady improvement has been seen in neonatal survival rates. This finding has shifted the limit of human viability progressively downward in gestational age (GA), although published survival rates for the smallest and most premature infants remain low. However, across similar time periods, reported rates of survival at 22 weeks' gestation in different countries vary dramatically. For example, survival rates are as low as zero in Switzerland to as high as 34% in Japan.<sup>1,2</sup> By 25 weeks' gestation, the range of survival rates is narrower but still wide: 61% to 67% in Switzerland and Australia, respectively, to 85% in Japan.<sup>1-3</sup> These differences have been attributed to either a more active interventionist approach or to underreporting of perinatal deaths.<sup>4-6</sup>

Many professional organizations and scientific societies in industrialized countries promulgate management guidelines for the extremely preterm infant. At the same time, an increasing emphasis on involving parents in decision-making encourages informing prospective parents of outcomes of morbidity and mortality, as well as the associated uncertainty of estimates.<sup>7,8</sup> Statements of recommendations by scientific and professional bodies are meant to facilitate decision-making. The present study assessed the variability between countries in such treatment recommendations for premature infants between 22 and 25 completed weeks of gestation in the world's most industrialized countries.

## **METHODS**

### **Literature Search**

We searched databases (Embase, PubMed, and Google Scholar) by using a combination of the following subject headings (Medical Subject Headings) and free text (textword): practice guidelines; OR perinatal care;

OR resuscitation AND infant, extremely low birth weight; OR infant, extremely premature; OR infant, extremely low gestation; OR limit of viability; OR viability. No language restrictions were applied. All potentially relevant titles and abstracts were retrieved and assessed for eligibility by 2 independent observers (U.G. and E.M.W.), and any disagreements were resolved by consensus. The reference lists of relevant articles were reviewed, and relevant citations were retrieved if they had not been obtained in the primary search. Reference lists of reviews, editorials, commentaries, and letters were also reviewed and retrieved if relevant.

### **Definition of Eligible Countries**

The United Nations Development Programme's Human Development Index (UN-HDI) is a comparative measure of life expectancy, literacy, education, standards of living, and quality of life for countries worldwide.<sup>9</sup> This tool is a standard means of measuring well-being (including child welfare) and is used to distinguish whether a country is developed, developing, or underdeveloped. Recommendations from the 47 countries categorized as very highly developed in the UN-HDI publication were eligible for the present study.

### **Eligibility Criteria**

Inclusion criteria were as follows: (1) the statement specifically addressed management for infants 22 to 25 completed weeks' GA; (2) the body drawing up the statement was a professional, government, or international body; and (3) the guideline was for a country, or group of countries, categorized by the UN-HDI as "very highly developed." Guidelines for individual hospitals or institutions were excluded.

### **Primary Outcome**

The primary outcome was the treatment recommendations for

infants at each week of gestation between 22 and 25 completed weeks' GA. GA was defined as the postmenstrual age in weeks and days, in which a completed week of gestation was the time period between the beginning of a specific week up to and including 6 days later. For example, the time period between 22 0/7 and 22 6/7 weeks' gestation was defined as 22 completed weeks. Recommendations were categorized independently by 2 reviewers (U.G. and E.M.W.) into 1 of 5 possible groups for each GA: (1) comfort care (includes comfort care only; comfort care unless infant emerges unexpectedly vigorous; comfort care in the absence of exceptional prognostic factors; and those specifying that active care may be discussed but should be discouraged); (2) parental wishes (recommendations clearly stated that parental choice must be followed for all infants at a particular gestation); (3) individualized (includes recommendations that a physician assess the infant at the time of birth before making a decision as well as resuscitation only if the infant appears viable at the time of birth); (4) active care (includes full resuscitation in all cases or full resuscitation unless other negative factors are present); and (5) no recommendations. If reviewers did not agree on classification, disagreements were reviewed and if needed adjudicated by a third reviewer (H.K.).

### **Secondary Outcome**

We assessed whether GA-specific survival rates were cited by the guidelines and whether these survival rates were specific to the country publishing the guidelines. We also assessed whether the guidelines considered the potential for 1 of 3 possible methodologic biases that can affect the discussion of whether an infant should be resuscitated. These biases were: (1) the limitation of accurate assessment of GA being

dependent on early ultrasound dating<sup>10,11</sup>; (2) variable definitions in the classification of a live birth versus a stillbirth<sup>12</sup>; and (3) so-called “denominator bias,” in which different denominators (all infants versus live births versus those surviving to neonatal unit admission) result in varying survival rates.<sup>13</sup>

## RESULTS

### Eligible Guidelines

Two independent searchers achieved very good agreement on the inclusion and exclusion of publications ( $\kappa = 0.844$ ) and on the extraction of data for the primary ( $\kappa = 0.965$ ) and secondary ( $\kappa = 0.939$ ) outcomes. All disagreements were resolved.

A total of 34 guidelines were identified, 30 of which represented 23 very highly developed UN-HDI countries, and 4 were guidelines from international professional bodies.

These guidelines encompassed countries from North America ( $n = 2$ ), South America ( $n = 1$ ), Europe ( $n = 16$ ), Asia ( $n = 2$ ), and Oceania ( $n = 2$ ). All except for 1 were published in the last 10 years. Recommendations from multiple professional organizations were found for the United Kingdom ( $n = 3$ ), the United States ( $n = 4$ ), Australia ( $n = 2$ ), and the Netherlands ( $n = 2$ ). The recommendations for Norway, Greece, and the Czech Republic were provided via personal communication but had either not been formally published or did not contain concrete data and were therefore not included. The present review thus included 31 guidelines from 20 different countries and 4 international professional bodies.

### Primary Outcome

There was a wide range of recommendations for the initial neonatal resuscitation (Table 1).<sup>1,14–43</sup> The key results are summarized in Fig 1 and show that recommendations are “anchored” at the 2 extremes of gestational age (22

**TABLE 1** Recommendations According to Week of Gestation

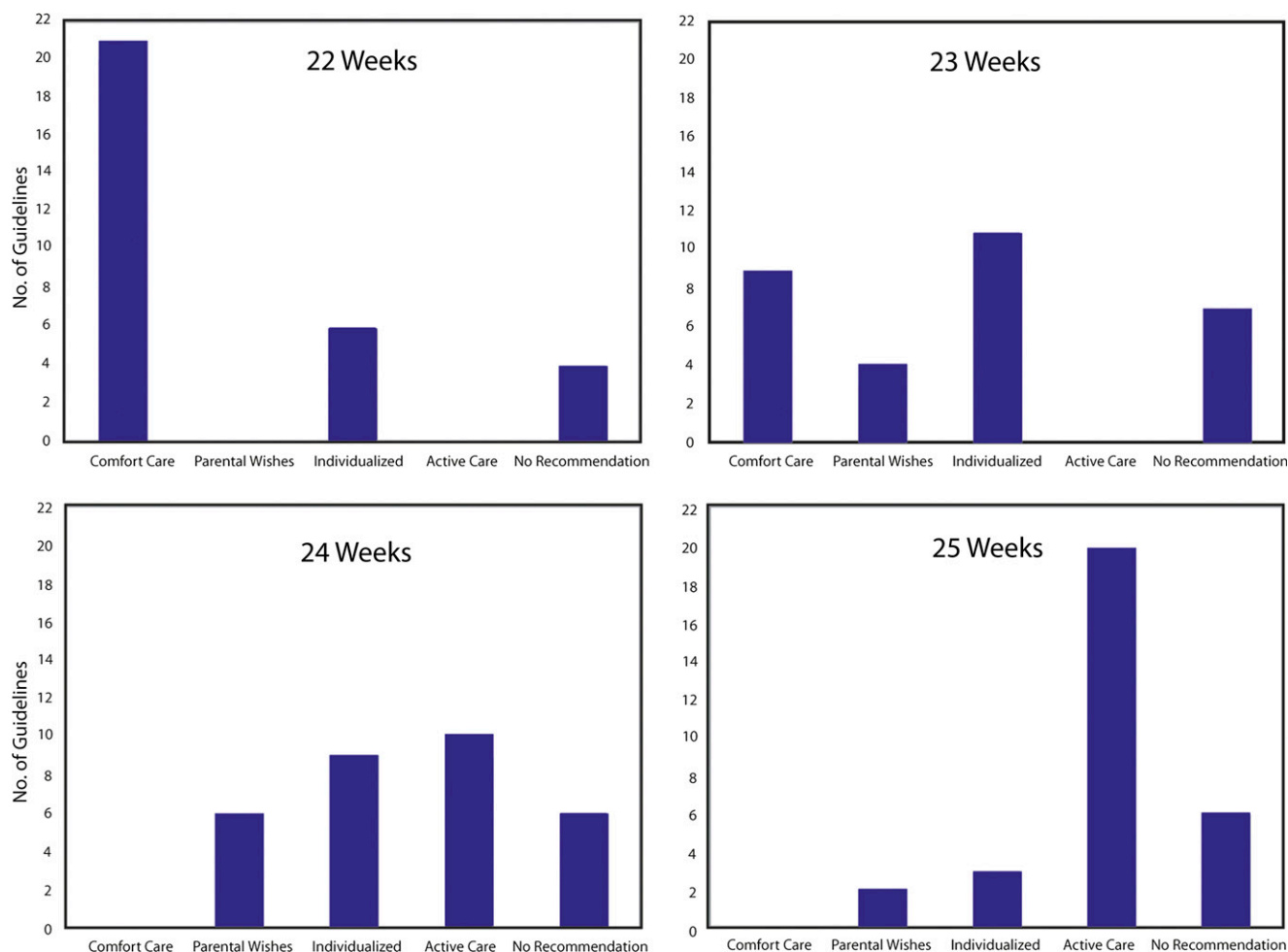
Country	Year	Weeks of Gestation				Potential Biases		
		22	23	24	25	Assessment	Definition	Denominator
Argentina <sup>14</sup>	2012	CC	NR	NR	NR	Yes	No	No
Australia <sup>15</sup>	2006	CC	CC	AC	AC	No	No	No
Australia <sup>16</sup>	2013	CC	PW	PW	AC	No	No	No
Belgium <sup>17</sup>	2014	CC	CC	PW	PW	Yes	No	Yes
Canada <sup>18</sup>	2012	CC	IND	IND	AC	Yes	Yes	Yes
Finland <sup>19</sup>	2014	IND	IND	AC	AC	No	No	No
France <sup>20</sup>	2010	CC	CC	PW	AC	Yes	Yes	No
Germany <sup>21</sup>	2008	IND	IND	AC	AC	Yes	No	No
FIGO, international association <sup>22</sup>	2006	NR	NR	NR	NR	No	No	No
ILCOR, international association <sup>23</sup>	2006	CC	NR	NR	NR	No	No	No
WAPM, international association <sup>24</sup>	2010	CC	IND	AC	AC	Yes	No	No
European Resuscitation Counsel, international association <sup>25</sup>	2010	CC	PW	PW	AC	No	No	No
Ireland <sup>26</sup>	2006	CC	CC	PW	PW	No	No	No
Italy <sup>27</sup>	2008	IND	IND	IND	IND	Yes	No	No
Japan <sup>28</sup>	2012	NR	NR	NR	NR	No	No	No
Dutch Pediatric Society, the Netherlands <sup>29</sup>	2006	CC	CC	IND	AC	No	No	No
Dutch Ministry of Health, the Netherlands <sup>30</sup>	2010	NR	NR	AC	AC	No	No	No
New Zealand <sup>31</sup>	2011	NR	NR	NR	NR	No	No	No
Poland <sup>32</sup>	2011	CC	CC	IND	AC	Yes	No	No
Portugal <sup>33</sup>	2012	CC	CC	AC	AC	Yes	No	Yes
Singapore <sup>34</sup>	1998	IND	IND	IND	AC	No	No	No
Spain <sup>35</sup>	2004	CC	NR	NR	NR	No	No	No
Sweden <sup>36</sup>	2004	CC	IND	IND	AC	Yes	No	Yes
Switzerland <sup>1</sup>	2011	CC	CC	AC	AC	Yes	No	No
Nuffield Council, United Kingdom <sup>37</sup>	2006	CC	PW	AC	AC	Yes	Yes	Yes
BAPM, United Kingdom <sup>38</sup>	2009	CC	CC	AC	AC	Yes	No	No
Royal College of Obstetricians and Gynaecologists, United Kingdom <sup>39</sup>	2014	CC	IND	IND	AC	Yes	No	No
AAP, United States <sup>40</sup>	2009	IND	IND	IND	IND	Yes	No	No
ACOG, United States <sup>41</sup>	2012	IND	IND	IND	IND	Yes	No	Yes
AHA, United States <sup>42</sup>	2010	CC	PW	PW	AC	No	No	No
Joint Workshop, United States <sup>43</sup>	2014	CC	IND	AC	AC	Yes	No	Yes

AAP, American Academy of Pediatrics; AC, active care; ACOG, American College of Obstetricians and Gynecologists; AHA, American Heart Association; BAPM, British Association of Perinatal Medicine; FIGO, International Federation of Gynecology and Obstetrics; ILCOR, International Liaison Committee on Resuscitation; IND, individualized care; CC, comfort care; NR, no recommendation; PW, parental wishes; WAPM, World Association of Perinatal Medicine.

and 25 weeks). None of the guidelines recommended active care at 22 weeks' GA, and none of the guidelines recommended comfort care at 25 weeks' GA. There were no such predominant recommendations at either 23 or 24 weeks' GA. At 23 weeks, recommendations included 29% ( $n = 9$ ) comfort care, 13% ( $n = 4$ ) following parental wishes, and 35% ( $n = 11$ ) individualized care. Twenty-three percent ( $n = 7$ ) did not make any recommendations, and none recommended active care at this gestation. At 24 weeks, recommendations were divided between 19% ( $n = 6$ ) parental wishes,

29% ( $n = 9$ ) individualized care, and 32% ( $n = 10$ ) active care. Nineteen percent ( $n = 6$ ) did not make any recommendations, and none recommended comfort care at this gestation.

There was agreement across the 3 professional organizations in the United Kingdom for the treatment of infants at 22 weeks' (comfort care) and 25 weeks' (active care) GA but no agreement at 23 and 24 weeks' GA. Similarly, in Australia, there was agreement for the treatment of infants at 22 weeks' (comfort care) and 25 weeks' (active care) GA but no agreement at 23 and 24 weeks' GA. In



**FIGURE 1**  
Recommendations between 22 and 25 completed weeks of gestation.

the Netherlands, both guidelines agreed with active care at 25 weeks' but did not have agreement at 22 to 24 weeks' GA. Two of the 4 US guidelines agreed about the management across 22 to 25 weeks' GA (individualized). The remaining 2 guidelines had agreement only at 22 weeks' GA (comfort care) and 25 weeks' GA (active care).

### Secondary Outcomes: Discussion of Potential for Bias

Survival rates according to GA were cited by 55% ( $n = 17$ ) of guidelines (Table 2).<sup>\*</sup> Excluding the 1 international group citing survival rates, 88% of those discussing

survival rates ( $n = 14$ ) included findings specific to their country. There was variation in how survival rates were reported. The denominator used for the reported survival rates (live births or NICU admissions) was not always clearly stated. When survival rates from multiple sources were cited, it was not always specified if all of these sources used the same denominator.

The limitations of accurate GA dating unless there was an early dating ultrasound was cited by 55% ( $n = 17$ ) of guidelines. Only 23% ( $n = 7$ ) of guidelines discussed the problems associated with denominator bias. Even fewer guidelines (10% [ $n = 3$ ]) discussed any potential bias from the use of different definitions for live births and stillbirths.

### DISCUSSION

There was a wide variation in recommendations across 31 guidelines in 20 very highly developed countries. However, this variation was relatively "anchored" (ie, being less variable) at 22 and 25 weeks' GA. At 22 weeks' GA, most guidelines encourage comfort care, and at 25 weeks' GA, most encourage active treatment. Variability is more marked with an apparent range of recommendations for infants between 23 and 24 weeks' GA. This area has been termed a "gray zone" of uncertainty.<sup>44,45</sup> The consistency of recommendations for 22 and 25 weeks' GA suggest an apparent consensus across several countries. In a few countries, individualized care or following parental wishes is

<sup>\*</sup>Refs 1, 15–18, 21, 24, 26, 30, 32, 33, 36–39, 41, and 43.

**TABLE 2** Percent Survival Rates According to Weeks of Gestation

Country	Weeks of Gestation			
	22	23	24	25
Australia <sup>15</sup>	0 <sup>a</sup>	29 <sup>a</sup>	50 <sup>a</sup>	65 <sup>a</sup>
Australia <sup>16</sup>	20 <sup>a</sup>	52 <sup>a</sup>	65 <sup>a</sup>	78 <sup>a</sup>
Belgium <sup>17</sup>	0 <sup>a</sup>	14 <sup>a</sup>	58.5 <sup>a</sup>	60 <sup>a</sup>
Canada <sup>18</sup>	0–34	9–54	26–76	44–85
Germany <sup>21</sup>	—	50 <sup>b</sup>	60	75
WAPM, international association <sup>24</sup>	1–15	8–33	26–51	—
Ireland <sup>26</sup>	—	10 <sup>c</sup>	—	—
Dutch Pediatric Society, Netherlands <sup>30</sup>	—	—	20–30 <sup>d</sup>	44–48 <sup>d</sup>
Poland <sup>32</sup>	—	6–26	26–55	44–77
Portugal <sup>33</sup>	0–1	10–11	26–50	44–61
Sweden <sup>36</sup>	0–21	2–46	17–59	35–85
Switzerland <sup>1</sup>	0–10	4–52	30–67	51–81
Nuffield Council, United Kingdom <sup>37</sup>	1	11–43	26–63	44
BAPM, United Kingdom <sup>38</sup>	1.5	11	26	44
Royal College of Obstetricians and Gynaecologists, United Kingdom <sup>39</sup>	16 <sup>a</sup>	29 <sup>a</sup>	46 <sup>a</sup>	69 <sup>a</sup>
ACOG, United States <sup>41</sup>	21	30	50	75
Joint Workshop, United States <sup>43</sup>	5–51	26–76	55–87	72–80

ACOG, American College of Obstetricians and Gynecologists; BAPM, British Association of Perinatal Medicine; WAPM, World Association of Perinatal Medicine.

<sup>a</sup> Survival rates cited as percentage of NICU admissions.

<sup>b</sup> Combined survival rates for 22 and 23 weeks' gestation.

<sup>c</sup> Combined survival rates for <24 weeks' gestation and <500 g birth weight.

<sup>d</sup> Survival rates reported as survival for infants  $\leq$ 24 weeks' gestation or 25/26 weeks' gestation.

recommended at 22 and 25 weeks' GA (6 and 5 recommendations, respectively). This outcome could be interpreted that in those countries, the gray zone of uncertainty extends to include those 2 weeks of gestation. Gallagher et al<sup>46</sup> found a similar phenomenon across 19 European countries. It is interesting to note that across the 4 countries for which we found multiple sets of guidelines (United Kingdom, United States, Australia, and the Netherlands), the professional associations did not agree with each other with respect to the treatment of infants at 23 and 24 weeks of gestation.

We found up to 7 country guidelines that did not make any recommendations for some specific weeks of gestation. For example, Spain recommended comfort care for infants at 22 weeks but did not make any recommendations at 23 to 25 weeks of gestation. It is possible that recommendations were not made in these countries because the default is active care in every case at those gestations. Conversely, in 1 of the 2 guidelines found for the Netherlands, active care was recommended for all

infants at  $\geq$ 24 weeks' GA, but there were no recommendations for 22 and 23 weeks' GA. On discussion with the author, we found that comfort care is assumed at those gestations. In these 7 countries, the lack of recommendations for specific weeks of gestation may also reflect a wide local variation in opinion of what is considered appropriate. Possibly, in the absence of a clinical consensus, national bodies may prefer to avoid making recommendations.

In clinician and parental decision-making, survival rates are often considered; however, these may be subject to interpretation. Framers of guidelines did not consistently take into account potential modifiers or biases, which perhaps reflected their wish to be succinct. Most guidelines cited survival rates to support their recommendations, which largely quoted their own specific country rates. This design is important because there is a wide variation in reported survival rates across countries.<sup>1–3,47</sup> A related interpretational issue is the dependence of survival rates on the denominator used. This so-called denominator bias describes higher survival when only live

infants admitted to the NICU form the denominator as opposed to when either all live births or all births are used.<sup>13,48</sup> This problem is difficult to quantify because the majority of published studies report only "survival rate" without further qualification.<sup>13</sup> Only 7 guidelines in our review explicitly acknowledged any potential for a denominator bias.

Many more guidelines acknowledged a potential bias arising from inadequate GA dating. It has been argued that because of the imprecision of GA estimates, it is illogical to base decisions about the care of infants at the limits of viability by using only this single factor.<sup>49,50</sup> However, other methods to establish pregnancy dating at 22 to 25 weeks' GA have not been reliable.<sup>51</sup> Moreover, maternal access to health care in several very highly developed countries is good enough that an early ultrasound dating GA is usually available.<sup>18</sup>

Another potential source for wide country variations in survival relates to the legal definitions to record stillbirths. Although the United States defines stillbirths as fetal deaths delivered at  $\geq$ 20 weeks' GA, stillbirths are defined as fetal deaths after at least 24 weeks' gestation in the United Kingdom and at least 28 weeks' gestation in Sweden.<sup>12</sup> Across industrialized countries, the registration of live births and stillbirths, especially at the limits of viability, vary widely and thereby affect reported survival rates.<sup>52,53</sup> Joseph et al<sup>12</sup> found wide variations in birth registration procedures across highly developed countries, especially in the reported rates of live births at the low end of the range of birth weight and GA. Variations in the registration of births at the borderline of viability affect comparisons of infant mortality between countries. It is thus important that only 3 of 31 guidelines acknowledged the potential bias in survival data from this difference. We also found that other prognostic factors which may impact an infant's chances

of survival and are routinely known before birth were not included in the guidelines.<sup>54,55</sup> Several statements noted the existence of other important prognostic factors such as gender, estimated fetal weight, birth number, administration of antenatal steroids, and maternal morbidities. However, none of the guidelines contained specific recommendations to guide practitioners on how they should incorporate these factors into treatment decisions.

This study was limited to guidelines from industrialized countries because the technical skills, resources, access to care, and short- and long-term high costs of caring for an extremely

premature infant may lead to different recommendations in low-income countries. It is unknown to what extent the professional body recommendations drive implementation of decisions by clinicians and parents, but we suspect they do have some influence. This situation has been termed the self-fulfilling prophecy in NICU care.<sup>56,57</sup> Nonetheless, we found wide variation in the specific recommendations for infants in the categories of 23 to 24 completed weeks of gestation. However, there was an apparent broad consensus for comfort care at 22 weeks' GA and active care at 25 weeks' GA.

## CONCLUSION

Although there is a wide variation in the recommendations across highly developed countries for the resuscitation of extremely premature infants, there is general agreement for comfort care at 22 weeks' GA and active care at 25 weeks' GA.

## ABBREVIATIONS

GA: gestational age  
UN-HDI: United Nations  
Development  
Programme's Human  
Development Index

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