

ORIGINAL ARTICLE

Limits of viability: definition of the gray zone

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Introduction: As survival and long-term morbidity of very preterm infants have improved over the past decade, the limits of infant viability, the level of maturity below which survival and/or acceptable neurodevelopmental outcome are extremely unlikely, have also decreased.

Study Design: In an effort to define the current limits of infant viability, the data in the literature on survival and long-term neurodevelopmental outcome in very preterm neonates have been reviewed.

Result: The gestational age and birth weight below which infants are too immature to survive, and thus provision of intensive care is unreasonable, appears to be at <23 weeks and <500 g, respectively. Infants born at ≥25 weeks' gestation and with a birth weight of ≥600 g are mature enough to warrant initiation of intensive care, as the majority of these patients survive, and at least 50% do so without severe long-term disabilities. Finally, for infants born between 23^{0/7} and 24^{6/7} weeks' gestation and with a birth weight of 500 to 599 g, survival and outcome are extremely uncertain. For these infants born in the so-called 'gray zone' of infant viability, the line between patient autonomy and medical futility is blurred, and medical decision-making becomes even more complex and needs to embrace careful consideration of several factors. These factors include appraisal of prenatal data and the information obtained during consultations with the parents before delivery; evaluation of the patient's gestational age, birth weight and clinical condition upon delivery; ongoing reassessment of the patient's response to resuscitation and intensive care and continued involvement of the parents in the decision-making process after delivery.

Conclusion: Based on these findings an algorithm is offered for consideration for neonatologists managing infants born in the 'gray zone' of infant viability. However, caution must be exercised when one considers incorporating this guideline into clinical practice because the algorithm is based on the analysis of the findings in the literature and the authors' experience rather than direct evidence.

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Introduction

Survival of preterm neonates has steadily improved over the past five decades.^{1–9} The gestational age at which at least half of the infants survive has decreased from 30 to 31 weeks in the 1960s to 23 to 24 weeks during this decade.⁸ The increase in survival of the smallest, most vulnerable infants represents an enormous improvement in our ability to deliver prenatal, perinatal and postnatal care to the pregnant woman and her offspring and could not have been achieved without close collaboration between perinatology and neonatology and advances in our understanding of fetal, transitional and neonatal physiology and pathophysiology. Although neurodevelopmental outcome of very preterm neonates has also significantly improved over this period,^{5–8} the pace of improvement in central nervous system morbidity appears to have lagged behind that of survival. In addition, neurodevelopmental impairment in infants born extremely immature persists into school age, and the level of impairment is often underestimated when standardized tests are being used for the assessment of these patients' cognitive and neurological status.¹⁰ Thus, data on survival and long-term neurodevelopmental outcome in very preterm infants are influenced by multiple factors and need to be carefully assessed. Adding to the complexity of this issue is the finding that very preterm neonates have a survival advantage if they are born at large perinatal–neonatal centers where caregivers have significant experience in providing perinatal and neonatal care and a comprehensive multidisciplinary operational structure is in place.¹¹

One of the fundamental challenges perinatal–neonatal medicine has had to address from its inception is to define the level of maturity below which survival and/or acceptable neurodevelopmental outcome are extremely unlikely. As for survival, the data are more readily available, as neonatal survival is

a clearly definable outcome occurring during the first 28 postnatal days or, in the case of survival to discharge, within the first few postnatal months. However, determining the extent of neurodevelopmental involvement resulting in unacceptable quality of life is very difficult if not impossible, since fulfillment of this criterion requires placing a value on 'quality of life' itself as well as a long follow-up period. This is further complicated by the fact that in the case of a newborn a surrogate (usually the parents) must define quality of life for the patient. This is an extremely complex and difficult task, as it requires reconciliation of two diabolically opposing factors; namely the instinct to do everything for the survival of our offspring and to overcome this most powerful instinct to consider a potentially painful and perhaps meaningless life, where suffering and dependency dominate existence. This complex parental decision-making is influenced by many factors, including, but not limited to, personal and religious beliefs, individual experiences, family environment, societal expectations and pressures, socioeconomic status and the level of education. The lack of a universally acceptable definition of 'quality of life' has also resulted in difficulties in interpreting long-term neurodevelopmental outcome data for the very immature patient population. Additionally, even if data of acceptable or good quality existed for long-term outcome measures in a given patient population, the findings may be outdated by the time they become available, as changes in clinical practice usually outpace the timeframe within which long-term data can be collected and published. Therefore, even if recently published 6- to 8-year outcome data were found to be discouraging or encouraging for a given patient population, the extent to which these findings apply to the current patient population is not known.

Before the available data are examined, it is necessary to define the current state of patient autonomy. In modern medicine, acceptance of a competent and informed patient's right to refuse offered medical interventions has become the norm. The only exception to this rule is when physicians invoke medical futility. 'Medical futility' refers to interventions that are unlikely to produce any significant quantitative or qualitative benefit for the patient. Quantitative benefit of an intervention is defined by the likelihood a given intervention will result in benefit, while qualitative benefit of an intervention refers to the quality of the benefit an intervention will produce. As for futility, quantitative or qualitative futility refers to the lack of prospect of a real benefit to the patient. For instance, a treatment that merely produces a physiological effect on a patient's body does not necessarily confer any benefit the patient can appreciate. Importantly, autonomy and futility in the area of infant viability do not meet at a well-defined line of maturity.¹² Rather, their interaction is characterized by the presence of a 'gray zone,' a wider range of gestational age.^{5,8,12} The goal of this paper is to define the current limits of infant viability with a special focus on the gestational age range of the 'gray zone,' where physician-patient (or surrogate) discussions,

negotiations and compromise may be the most appropriate model for consensus development or conflict resolution.¹³ In addition, the authors offer a nonevidence-based algorithm the practicing neonatologist may consider when facing the prospect of caring for infants in the 'gray zone' of infant viability.

Results and Discussion

Most clinicians and investigators agree that applying the concept of the 'gray zone' is best suited to define the limits of viability for the most immature patient population.¹² Below the lower limit of the 'gray zone,' the infant is too immature to have any reasonable chance for survival without severe deficits. For these infants, provision of care other than comfort care is unreasonable. Above the upper limit of the 'gray zone,' however, the infant is mature enough to have a reasonable chance for a good outcome, therefore initial aggressive care is the norm, at least until the patient's response to treatment can be objectively assessed. For patients falling within the 'gray zone,' careful consideration of certain additional factors and constant reevaluation of the effect of the treatment in the delivery room and later in the neonatal intensive care unit (NICU) are recommended.

Definition of the 'gray zone'. Assignment of patients to the 'gray zone' hinges on several factors, including our ability to correctly assess the given patient's gestational age before and, most importantly, immediately after delivery and to perform meaningful prenatal consultations with the obstetrician and the family. Thus, the neonatologist must be involved in the decision-making process before delivery and attend the delivery of every neonate near the limit of viability to assess the patient's gestational age and evaluate the patient's condition upon delivery.

Available data indicate that survival of appropriate-for-age infants <23 weeks' gestation and <500 g birth weight is extremely unlikely, with virtually no chance for intact survival.^{6,8,14-17} Importantly, these data have not changed substantially over the past 10 to 15 years.⁸⁻¹² In an earlier study, although approximately 10% of neonates born at 22 weeks' gestation survived to admission to the NICU, none of them were alive by 6 months of age.¹⁸ In more recent studies, none of the infants born at <23 weeks were reported to survive to discharge from the NICU.¹⁹⁻²⁰ It appears that these findings, and perhaps the practicing neonatologists' own experiences, have influenced the approach to the management provided in the delivery room to the smallest and most immature neonates, as a recent survey of academic and private neonatologists in the United States has found that only 4% of the participants would resuscitate a neonate at 23 weeks' gestation with a birth weight of <500 g.¹² It further states that 57% of the responders would provide comfort care only, and 36% would defer the decision to parental wishes for these extremely immature infants.¹² Data from the Vermont-Oxford Network's database covering a 5-year period at the end of the

past decade reveal that survival to discharge among 4172 infants with a birth weight between 401 and 500 g and a gestational age of 23.3 ± 2.1 weeks was only 17%.²¹ Of note is that this paper did not report survival to discharge according to gestational age; it used birth weight instead as it is a more accurately definable variable for a retrospective study querying a large database. Factors associated with successful delivery room resuscitation and admission to the NICU as opposed to death in the delivery room for this patient population included small-for-gestational age status, being delivered via cesarean section, female gender and exposure to prenatal steroids.²¹ From the available data, one can conclude that preterm neonates born at <23 weeks' gestation and with a birth weight of <500 g are too immature to survive with current technology and, therefore, provision of care other than comfort care is unreasonable, even if the parents wish to have everything done for the patient. Again, this statement assumes that gestational age has been appropriately assessed using early prenatal ultrasonographic data and/or the findings of a comprehensive physical exam performed by an experienced neonatologist after delivery. It also assumes that a prenatal consultation ensuring appropriate exchange of information between the parents and the neonatologist has taken place.

Contrary to the outcome of infants born at <23 weeks' gestation and with a birth weight of <500 g, preterm neonates born at ≥ 25 weeks' gestation and ≥ 600 g have a survival rate of over 60 to 70%, and as many as 50% or more of the survivors have no evidence of severe disability defined as nonambulatory cerebral palsy, mental retardation, severe visual or hearing deficit, or a combination of these neurodevelopmental impairments upon long-term follow-up.^{6,8,9,14-17,19} As for the present clinical practice in the United States, findings of the earlier-cited survey¹² indicate that for infants with a gestational age of 25 weeks and a birth weight between 600 and 750 g, 91% of practicing neonatologists would initiate full resuscitation, while 8% would defer to the parents' wishes and 1% would provide comfort care only. In summary, the available information in the literature on mortality and long-term neurodevelopmental morbidity indicate that infants born ≥ 25 weeks' gestation and ≥ 600 g are mature enough to justify full resuscitation and intensive care and that the overwhelming majority of neonatologists in the United States will provide this level of intervention.¹²

Taking these data together, infants born at 23^{0/7} to 24^{6/7} weeks' gestation and with a birth weight of 500 to 599 g fall between those who are clearly too immature to survive^{6,8,12,14-20} and those who

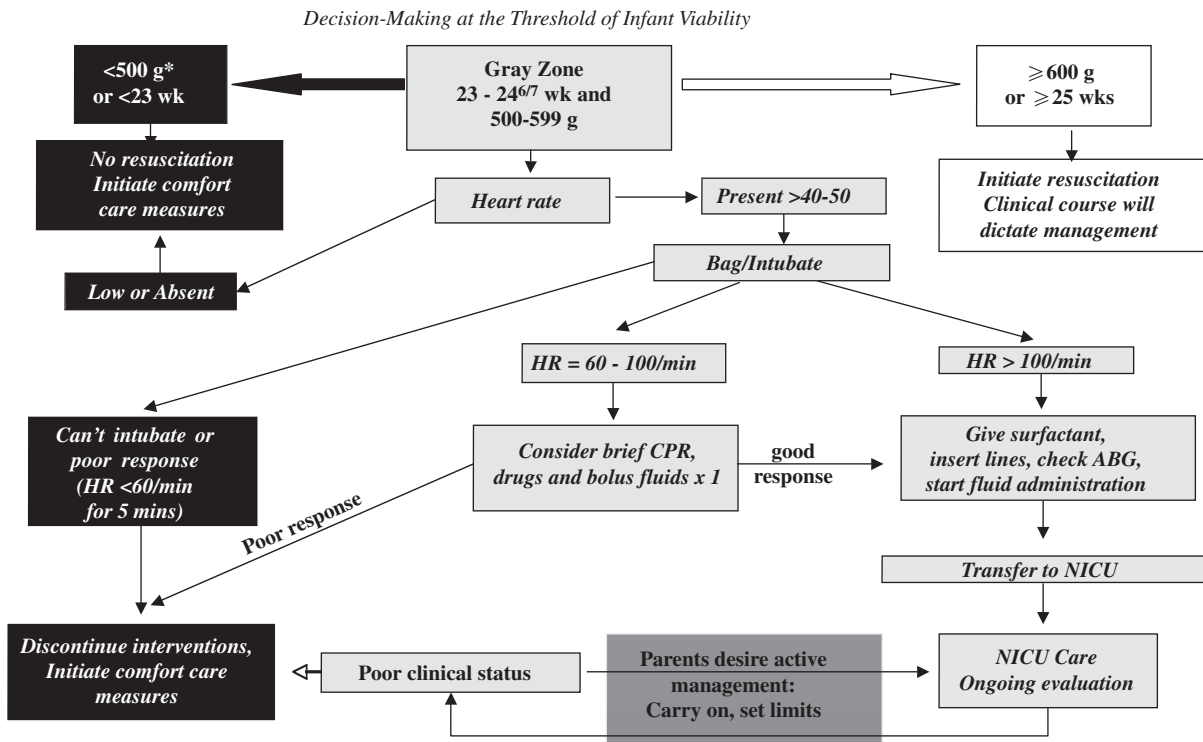


Figure 1 Since the patient's condition upon delivery significantly impacts survival and probably long-term morbidity in infants in the 'gray zone' of infant viability, for patients born without a heart rate, provision of comfort care only may be appropriate. If the infant's condition is severely compromised, provision of brief resuscitation with ongoing assessment of the patient's response to treatment may be warranted. Even if the infant is vigorous at birth or responds to resuscitation and survives to admission to the neonatal intensive care unit (NICU), ongoing evaluation and parental involvement in the decision-making process are recommended. Infants with a birth weight of <500 g who are vigorous at birth probably warrant active intervention, as they are likely small-for-gestational age (*). It is important to note that this algorithm is based on the analysis of the data in the literature and the authors' experience and clinical practice rather than direct evidence. See text for details.

are mature enough to have reasonable outcomes.^{6,8,9,13,14–17,19} Thus, these patients fall within the ‘gray zone’ of infant viability, where survival and long-term outcome are overall very poor for the group but very difficult to predict, and possibly acceptable for the individual patient.²² In the ‘gray zone,’ the line between patient autonomy and medical futility becomes blurred and extends across the proposed range of gestational age. However, as the ‘gray zone’ represents a range of gestational age and thus level of immaturity in human development, survival and outcome even within this relatively narrow range may differ greatly according to the patients’ level of maturity and under certain other conditions. Indeed, the most immature infants in the ‘gray zone’ appear to be extremely susceptible to adverse pre- and perinatal factors affecting their clinical condition upon delivery. Although survival of uncompromised 23 weeks’ gestation neonates is very similar to that of uncompromised 24 to 25 weeks’ gestation infants and may be over 75%, 23 weeks’ gestation infants who are compromised upon delivery have a significantly decreased survival (<10%) compared to their compromised 24 to 25 weeks’ gestation counterparts (~50%).² These findings lend further support to the notion that a neonatologist needs to attend the delivery of every infant born at the limits of viability to be in the best position to make a decision about the most appropriate course of action. In addition, the information on the impact of the infant’s condition at delivery on survival needs to be discussed with the parents whenever possible before delivery so that they can appreciate the complexity of the situation and understand the limits of our ability to make a definite decision before delivery about how to proceed in the immediate postnatal period with infants born in the ‘gray zone’ of viability.

We offer an algorithm for the practicing neonatologist to consider when all the options are being contemplated as the family and the caregivers face the extremely difficult situation of the impending delivery of an infant at the limits of viability (Figure 1). This algorithm assumes that appropriate antenatal counseling has taken place, that gestational age was determined antenatally and has been reassessed upon delivery by a neonatologist and that birth weight was obtained at delivery. In addition, at each stage of the resuscitation, the prognosis for reasonable outcome needs to be reevaluated. Parental wishes regarding the extent of intervention in the gray zone should always be honored given the uncertainty of outcome, unless there is evidence that the parents do not represent best interests of their infant. When there are potential conflicts between medical and parental points of view, continued information exchange, negotiation and compromise are probably the best approaches for resolution of the conflict.¹³ It is these authors’ clinical practice that if there are significant outstanding issues such as uncertainty, about the infant’s gestational age and/or there is an unresolved conflict between the medical and parental plans, provision of clinical care will continue, the outstanding questions will be addressed and the infant’s condition will be

reassessed during the subsequent steps of management. This approach is recommended because discontinuation of life support is an option along the clinical course in these cases, while re-initiation of care after resuscitation or life support has been discontinued is a situation that must be avoided.

In summary, on the basis of available data in the literature, it is proposed that infants born at <23 weeks’ gestation and <500 g are too immature to survive and provision of care for these patients is unreasonable. On the other hand, infants who are born at ≥ 25 weeks’ gestation and with a birth weight of ≥ 600 g are mature enough and warrant initiation of intensive care. For infants born with gestational age and birth weight between these two groups, survival and outcome are uncertain and difficult to predict for the individual patient. For these infants in the ‘gray zone,’ medical decision-making should be based on careful evaluation of prenatal data and their gestational age, birth weight and clinical condition upon delivery. Finally, because uncertainty of outcome is the rule rather than the exception for these infants, parental involvement in the decision-making process before and after delivery and continuous reassessment of the patient’s response to intensive care should be the norm of the medical management.

Disclosure

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