PostScript

LETTERS

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Hypoxaemia in children: "abnormal" values may be misleading

Duke *et al* are to be commended for their interesting report aimed to determine normal oxygen saturation values in healthy infants and children and to assess the performance of clinical signs for predicting hypoxaemia in sick neonates and children with and without acute lower respiratory infections (ALRI).[1]

Acute lower respiratory infections (ALRI) account for a substantial burden of disease in children and adults, pneumonia being the leading cause of deaths in children under five, particularly in developing countries. Tachypnoea and chest retraction have been shown to be the most useful clinical signs for determining the presence of pneumonia and thus they are widely used in the diagnosis and management of this condition in children.[2] The World Health Organization pneumonia case detection and management programme,[3] which relies on these simple signs, seems to be justified by the existing body of evidence.

Varying degrees of hypoxaemia may be present in children with pneumonia. However, surprisingly few studies have been performed to assess normal values of haemoglobin oxygen saturation (SpO2) through the use of transcutaneous pulse oximetry, at both sea level and high altitude. Singhi's response to Duke *et al* rightly emphasises that altitude of studies reported must be taken into account in the interpretation of their results.[4] There are some reports on SpO2 values at mid- and high altitude settings in healthy and sick children.[5–8] We previously reported normal values of SpO2 in 1264 healthy children and adolescents living at 4100 m.[9]

The main conclusions of these studies performed at different altitudes are: firstly, values considered abnormal at sea level are very frequently found at high altitude in healthy children; secondly, normal values vary for different altitudes; thirdly, recommended SpO_2 cut offs for giving supplementary oxygen to sick children at sea level are clearly not applicable to high altitude settings, as according to these recommendations oxygen should be administered for values below 92%.[2] There is a need to perform more studies for determining which cut off values for supplementary oxygen are related to better outcomes in sick children living at high altitude. Moreover, our study at 4100 m revealed that SpO_2 values may be different according to different ethnic groups and history of exposure to high altitude. Higher SpO_2 values in Quechua children suggest a better degree of adaptation to high altitude in native populations with a longer time to exposure to high altitude. This latter finding has obvious practical implications, as high altitude native children, with higher baseline oxygen saturation levels than newcomers or resident non-native children, may need oxygen at higher cut off SpO_2 values when they are sick.

Singhi is justifiably concerned on the cost of giving oxygen to children who may not need it. Oxygen may be unacceptably expensive for health services in developing countries, particularly at primary level, where most sick children seek health care. However, hypoxaemia may be a serious, life threatening problem in sick children, particularly at high altitude, and thus we need to extend the study of Duke *et al* for different altitudes, in healthy and sick infants and children, to determine normal values of SpO_2 and to identify highly predictive clinical signs of hypoxaemia. The potential aggravating role of co-existing prevalent childhood diseases other than ALRI, namely diarrhoea, malnutrition, malaria, and HIV/AIDS, is also an area that warrants more attention. These data will allow providing both good quality and cost effective health care to sick children with and without ALRI.

Millions of children and adults live at high altitude. Developing a medicine based on scientific evidence that can be applicable to this setting is a major public health challenge for all of us working in those parts of the world.

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Response to Duke *et al*

We read with interest the article by Duke *et al*[1] regarding hypoxaemia in acute respiratory and non-respiratory illnesses in infants and children in developing countries published recently in *Archives*.[1] The authors have rightly pointed out the limited availability of published data on the incidence, significance or clinical signs predicting hypoxaemia in infants less than three months of age. With similar concerns we had conducted a study in infants less than two months, a part of which was published in the *Archives*.[2] We found that tachypnoea, defined as RR>60/min, predicted hypoxia with 80% sensitivity and 68% specificity.[2] In that study we had also examined six functional and behavioural responses as predictors of hypoxemia (table 1). Five of these six variables had a very good sensitivity to detect hypoxaemia.

A very high prevalence of hypoxaemia in the population studied by Duke *et al* is rather intriguing. Out of total 257 sick neonates and children 52%, were hypoxaemic. Among children with acute lower respiratory infection (ALRI) 73% and those with non-ALRI 32% were hypoxaemic. In an ongoing study we have measured oxygen saturation (by Nellcore® oximeter) in a prospective cohort of 683 children 2–59 months brought to paediatric emergency department (ED) with any respiratory symptom. Oxygen saturation using a fingertip sensor in these children at the time of arrival to ED ranged from 78–99%. The overall prevalence of hypoxaemia defined as SpO_2 <90% was 4.5% (table 2).

An additional 5.1% children had borderline hypoxaemia, i.e. a SpO_2 value of 90%. This is similar to a prevalence of 5.9% hypoxaemia (defined as SpO_2 <90%) in Gambian children, 2–33 months of age, reported by Usen *et al*.[3] Even in our previous study of 200 infants less than two months, only 38.5% of the sick infants attending ED were hypoxaemic.[2] A systematic review of studies on prevalence and predictors of hypoxemia in children by Lozano *et al*[4] found that the prevalence of hypoxia was dependent upon a number of factors including the setting of the study. The prevalence ranged from 6–9% in outdoor setting to 31–43% in emergency departments to a maximum of 47% in hospitalised children.

Yet, in our study, which represents the situation near sea level (Chandigarh being a plain topographically) and the setting of an emergency department, the prevalence of hypoxaemia is much lower than that reported at heights. In light of our data and published literature. We believe that either the definition of hypoxemia used by Duke *et al*[1] is too liberal or the children with respiratory symptoms living at high altitude decompensate more frequently to develop hypoxia. More information is needed in this respect to formulate

guidelines for general use. The cumulative data clearly suggest that hypoxaemia is more frequent in children living at high altitude. Interestingly most studies including that of Duke *et al* on this subject in children 2 to 59 months have been from high altitudes. It is most likely that geographic location, 1600m above sea level is responsible for the high frequency of "hypoxaemia" in their patient population. This, however, may not necessarily reflect the need for oxygen therapy. If definition of hypoxemia suggested by Duke *et al* were to be applied as a guideline to oxygen therapy almost half of their patients would need oxygen therapy. We need to answer as to whether oxygen therapy makes any difference to outcome of patients labeled as hypoxaemic using cut off limits proposed by Duke *et al*. It may also be worthwhile to conduct studies with a large sample size at sea level (plains) and in various settings before reaching a conclusion about SpO_2 cut off for hypoxia at heights.

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Hypoxaemia in developing countries

Drs Huicho, Singi, and Bharti make the important points that definitions of hypoxaemia should be based on altitude-specific normal values and that further research at sea level and higher altitudes is needed. An altitude-specific definition of hypoxaemia (being an arbitrary value of SpO_2 more than 2[1] or 3 standard deviations below the normal population mean) may be different from the threshold SpO_2 for giving oxygen. Other considerations for giving oxygen are at what level of SpO_2 (at different altitudes) oxygen is beneficial, local resource availability, and, in an individual child, confounding factors including the duration of exposure to altitude, age, or co-existent disease such as brain injury, severe anaemia, pulmonary hypertension, and cardiac failure.

We studied Papua New Guinean neonates and children living at an altitude of 1600m to determine normal range of oxygen saturation.[2] Hypoxaemia in our study was a SpO_2 more than 2SD below the mean. In practice our threshold for giving oxygen to sick children (SpO_2<85%: more than 3SD below the mean) was lower than this because of limited oxygen availability. However there is evidence that this is safe and effective.[3] We stated that without further evaluation this should not be applied to hospitals at substantially lower altitudes than 1600m or in areas where oxygen availability is greater.

In comparing the prevalence of hypoxaemia between studies in different health facilities referral and selection biases are likely. Hypoxaemia will be more common in emergency departments of referral hospitals than at primary care settings, and more common still among children requiring hospital admission.[4] The prevalence of hypoxaemia in hospitalised children will depend on thresholds for admission and case-mix. The 491 children in our study constituted about 20% of all the children admitted during the course of the study. A specialist paediatrician, whose practice was to oversee the care of sicker children, enrolled many of the patients, so this was a further source of selection bias. The much lower overall prevalence of hypoxaemia seen by Drs Singhi and Bharti in their emergency department population is therefore understandable. Of note the prevalence of hypoxaemia among sick neonates admitted to Goroka Hospital (43%) was similar to the prevalence among young infants (<2 months of age) attending the emergency department in Chandigarh (38.5%).[5]

It is interesting to consider the effects of altitude on hypoxaemia in children with pneumonia. Some populations living at higher altitudes have a greater tendency to pulmonary hypertension; this susceptibility may be genetically determined[6] and supports Dr Huicho's statement that ethnic differences in SpO_2 at the same altitude are important. At altitude in response to hypoxaemia, pulmonary blood flow is shunted to the lung apices associated with an exaggerated vasoconstriction in the basal lung.[7] This may have an adverse effect on ventilation perfusion matching in the supine position. In addition cardiac expression of natriuetic peptides increases in parallel with pulmonary artery pressure.[8] These and other pathophysiological changes may account for the greater severity and prolonged duration of hypoxaemia seen at higher altitudes.[3 9 10] It may be useful to evaluate the simple intervention of nursing children with pneumonia and hypoxaemia at high altitude in an inclined head-up position, rather than supine, to determine if this reduces the severity of hypoxaemia. There is a need for more evidence about the prevalence of hypoxaemia at sea level and different altitudes; which children benefit from oxygen; for how long oxygen should be given and the best ways to deliver oxygen in remote settings. Controlled trials of oxygen in mild hypoxaemia may not be justified for ethical reasons, but other evidence will be informative. Before the introduction of pulse oximetry in Goroka we used the World Health Organization guidelines for giving oxygen (cyanosis, inability to feed or severe respiratory distress). With the introduction of pulse oximetry we set a threshold for giving oxygen at SpO2 85%. The severe pneumonia case-fatality rate fell from 10% (26 / 258) pre-pulse oximetry to 5.8% (65/1116) 2 years later.[3 10] In highland PNG children cyanosis was only detected in 44% of those with an SpO_2 70–84%.[3] Although there will be confounders in the before-and-after analysis of outcome, we conclude that clinical signs must miss a significant proportion of children who would otherwise benefit from supplemental oxygen, and adherence to a protocol for the administration of oxygen based on a threshold SpO2 of 85% (more than 3 SD below the mean for normal children in Goroka) resulted in improved outcomes, and was within available resources.

The costs of oxygen and logistics of transporting cylinders are major problems in many developing countries; Dr Huicho is right that these are important public health challenges. They call for innovative research and development into how best to supply oxygen to children who need it. The role of oxygen concentrators need to be further explored;[11] the combination of concentrators with pulse oximetry would be appropriate technology for many hospitals in developing countries. Increasing the availability of any drug that is crucial to the management of more than 20% of children hospitalised worldwide should be a very high priority; oxygen is one such drug.

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Refugee children: don't replace one form of severe adversity with another

We strongly agree with Fazel and Steinn's view that refugee families require help that is culturally sensitive.[1] Failure to provide appropriate interventions in a culturally sensitive way to these children and their families means we potentially replace one form of severe adversity with another. Contrary to Fazel and Stein's positive view of school such adversity may include, for some children, integration into the UK educational system.[2]

While we agree that psychopathology can be identified in significant numbers of refugee children, many will have qualities of "resilience" that will have been highly developed by their experiences of war and other adversities prior to their arrival in this country. Having

already contributed so much to their own survival it is inappropriate to perceive refugees simply as victims who require help. Conventional Western responses may be thus inappropriate and ineffective; we need to provide a range of services that are both flexible and innovative. Papadopoulos' work with Bosnian refugee families is an excellent example of therapeutic innovation.[3] He has referred to "therapeutic presence" and "therapeutic witnessing" as opposed to formal psychotherapy. All of these children have a story to tell although for some the story will be more coherent than for others. In Western psychological terms their plight is somewhat comparable to that of abused children in the care system. Making sense of their experiences in a coherent way is a significant developmental task for them.[2] It is also potentially a shared experience as it is something these children will have in common with others in their family, peers, and wider refugee community. Life story work is an area in which many child mental health professionals, working with abused children, already have considerable expertise. Finally we would like to draw attention to the importance of a developmental approach when working with refugee children. It is a mistake to assume that their development parallels that of children growing up in the UK. Developmental pathways, as well as having occurred in a different cultural context, may have been significantly, and sometimes adversely, influenced by war and refugee experiences.

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Pharmacogenomic can give children safer medicines

I read with great interest Clarkson and Choonara's paper on the fatal suspected adverse drug reactions (ADRs) in the UK, and I strongly agree with their conclusions, namely that an evidence based approach to drug treatment is needed to minimise fatalities due to drug toxicity in children.[1] However, recent evidence also suggests that we are now ready for a gene based approach to drug treatment allowing to further minimise the occurrence and the severity of adverse drug reactions.[2] Increasingly complex genetic knowledge can already be used to elucidate mechanisms underlying the adverse events of drugs, to identify biomarkers for physiological events, and potentially even to predict adverse events before human exposure.[3]

In a recently published systematic review, the authors found that more than half of the drugs cited in ADR studies are metabolised by at least one enzyme with a variant allele known to cause poor metabolism, suggesting that genetic variability in drug metabolising enzymes is likely to be an important contributor to the incidence and severity of ADRs.[4] In Clarkson and Choonara's paper it is reported that anticonvulsants was the group of drugs most frequently associated with fatal ADRs.

Anticonvulsants are indeed among the drugs mostly concerned by enzymes with variant alleles associated with poor metabolism. A number of polimorphisms in the cytocrome 450 enzymes (CYPs), important in the metabolism of anticonvulsants have been reported. For example, the enzyme CYPIA2, which is one important metabolic pathway for carbamazepine and phenitoin, has only one identified variant allele with poor metabolism, but there is a significant prevalence of poor metabolisers for CYPIA2 among the general population. Other common polymorphisms concern the enzyme CYP2C19, resulting in altered metabolism of both phenobarbital and phenitoin.[5]

Substantial investments are being made within the pharmaceutical and biotechnology industries to use genomic strategies for the development of therapeutic agents targeted for specific subgroups of the population. Such pharmacogenomic studies also permit a more rational and safer use of existing therapies. It is my hope that this translation of functional genomics into rational therapeutics will not neglect the right of children to receive safer and more efficient pharmacotherapy, and that the pace of this transformation will not be limited by the lack of adequate pharmacogenomic information to practising paediatricians.

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Ketoacid levels may alter osmotonicity in diabetic ketoacidosis and precipitate cerebral edema

Inward and Chambers[1] have called for a rethink of the management of diabetic ketoacidosis. In their article they quote a study by Grove L M and colleagues[2] suggesting that pediatricians overestimated the quantum of dehydration in DKA. Over correction of dehydration is implicated in precipitating cerebral oedema. On the face of it, it seems implausible that pediatricians who are so adapt at estimating dehydration in the context of gastroenteritis, diarrhea, and vomiting should err in estimating the dehydration in DKA, unless the dehydration of DKA has special features. Hypertonicity may be that special feature. We hypothesize that hypertonic dehydration can result in the tongue appearing dry and parched and when this is combined with acidotic respiration of DKA, the treating pediatrician may classify the child as more severely dehydrated than he or she actually is.

In a study of DKA we found that the mean osmolality at admission was 318 (SD 12.9; range 291–337).[3] Further, we also found that the calculated osmolality (calculated osmolality=1.86(Na + + K +) + Urea + Glucose)[4] was only 289 (range 282–304). This suggests hypertonicity is common in DKA and calculated osmolality underestimates the true osmolality. The mean osmolar gap was 29 (range 14–48). The osmolar gap between true and the calculated osmolality, is made up of unmeasured substances like ketoacids. The osmolality of ketoacids have been ignored in the past, as they are considered to be osmotically inactive and not contributing to osmotonicity.[5] A study done by us (submitted for publication) has demonstrated that ketoacids (acetoacetates) are osmotically active. (Acetoacetate can influence fluid shifts across a semipermeable membranes. This is in contrast to urea, which is not osmotically active.)Osmolality, osmolar gap, and ketone bodies are not measured routinely during the management of DKA. A rapid fall in ketone body level can result in a fall in osmolality and osmoticity of the serum and lead to cerebral edema. In a recent paper looking at the risk factors for development of cerebral edema in DKA[6] the author noted that since none of the "relevant variables" (serum glucose concentration at presentation, change in serum glucose concentration during therapy, rate of fluid and sodium administration) were associated with the risk of cerebral edema, their data did not support the theory that a rapid decrease in extra cellular osmolality during treatment results in osmotic mediated swelling. Osmolality and osmolar gap were not measured, nor was ketone body levels studied (personal communication, Glaser N). Our studies demonstrates that the ketone level is probably a "relevant variable" that needs to be estimated before we can be certain that rapid decrease in extracellular osmolality did not occur. In summary we suggest that changes in ketone body levels be considered, as a factor that can be partially responsible for the cerebral edema often seen during treatment of DKA. We will be glad to share our data at any summit of experts convened to study the enigma of cerebral edema in DKA.

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BOOK REVIEWS

The Lazarus case, Life and Death Issues in Neonatal Intensive Care

John D Lantos. The Johns Hopkins University Press, 2001, pp 178. ISBN 0–8018–6762–2

When things go badly wrong in the perinatal period there has developed a culture in many "advanced societies" that demands a search for someone to blame. This search for guilt, accountability, punishment, and recompense often results in litigation.

In this thought provoking book John D Lantos describes such lawsuits as "our public morality plays" and uses his experience as a neonatologist, expert witness, and ethicist to create, debate, and crystallise relevant issues of ethics related to the neonatal intensive care of a fictional preterm infant who should have died but did not—*The Lazarus Case*.

A fictitious neonatologist, Dr Miller, decides to stop resuscitation of a very preterm infant who seems past reasonable care. The baby who might have died survived with severe neurological problems and the parents sue Dr Miller, alleging that stopping treatment was negligent. John Lantos places himself in the role of expert witness and uses questions put by the plaintiff's lawyers to explore the moral, ethical, legal, and social factors and to illustrate the ambiguities, misunderstandings, responsibilities, and evasions highlighted by the perinatal care of a 25 week gestation infant.

A key question put to Dr Lantos by one lawyer was "Can studying philosophy tell you whether what a doctor does in a particular case is right or wrong?" Probably not is the final conclusion reached by Dr Lantos, but it was just as unlikely that definitive guidance would come from sociology, religious doctrine, strict medical protocols, or any other single source.

There have been many attempts over the past half century to face and explain the moral dilemmas associated with our attempts to save the lives, prevent damage, and encourage optimal development of critically ill preterm infants. *The Lazarus Case* reviews in a most effective, compelling, erudite, and compassionate way the enormous complexity of these issues. It is highly recommended to all who are concerned with the care of preterm infants and their families and is essential reading for those required to provide medico-legal advice on life and death issues in neonatal intensive care.

Forrester Cockburn

Problems in Paediatric Drug Therapy, 4th edn

Edited by L A Pagliaro and A M Pagliaro. Washington: AphA 2002, $99.00, pp 829. ISBN 1 58212001 3

There is increasing interest in both the clinical and scientific aspects of drug therapy in paediatric patients. This text book by the American Pharmaceutical Association is aimed at the North American market.

It is a reference book aimed at paediatric pharmacists. It covers a wide range of the problems associated with paediatric drug therapy, with chapters on the administration of drugs, fetal toxicity, drugs in breast milk, and both poisoning and drug toxicity, and also specific clinical areas, for example chemotherapy. There did not appear to be any order in the chapters. It would seem more appropriate to put chapter 13 on neonatal doses after chapter 3 on drugs in breast milk than after a chapter on chemotherapy.

There are several chapters with information on the dosage of medicines and it is of interest that these are divided into three separate chapters, one for neonates, one for infants/children and adolescents and one specifically for intravenous drugs. Despite having a chapter specifically on intravenous drugs, the chapters on drug dosing on both neonates and infants/children and adolescents contains details on the doses required for intravenous administration. This makes the book far more difficult to use. The dosage guidance is far less user friendly than publications such as Medicines for Children or the Neonatal Formulary.

It is for this reason I would not therefore recommend Paediatric Pharmacy departments to buy a copy of the book.

I Choonara