Phototherapy is the current “drug” of choice to reduce the severity of neonatal unconjugated hyperbilirubinemia regardless of its etiology and its implementation requires a technical framework that conforms to existing guidelines that promote its safer and effective use (1). Optimal use of phototherapy has been defined by specific ranges of total serum bilirubin thresholds configured to an infant’s postnatal age (in hours) and potential risk for bilirubin neurotoxicity (1). Effective phototherapy implies its use as a “drug” at specific blue light wavelengths (peak, 460 to 500 nm) and emission spectrum (range, 400 to 520 nm), preferably in a precise (narrow) bandwidth, that is delivered at an irradiance (dose) of \( \geq 30-35 \mu\text{W/cm}^2/\text{nm} \) to upto 80% of an infant’s body surface area (BSA). Radiation with visible light above about 500 nm is considered useless.

Clinical response to a specific phototherapy modality is dependent on a number of confounding factors that include ongoing rate of bilirubin production and maturation of enterohepatic elimination processes. As described by Maisels and McDonagh (2), the absorption of light by the normal form of bilirubin (4Z,15Z-bilirubin) generates transient excited-state bilirubin molecules. These fleeting intermediates can react with oxygen to produce colorless products of lower molecular weight, or they can undergo rearrangement to become structural isomers (lumirubins) or isomers in which the configuration of at least one of the two Z-configuration double bonds has changed to an E configuration. (\( Z \) and \( E \), from the German \textit{zusammen} (together) and \textit{entgegen} (opposite), respectively, are prefixes used for designating the stereochemistry around a double bond. The prefixes 4 and 15 designate double-bond positions. Only the two principal photoisomers formed in humans are well described (3). Configurational isomerization is reversible and much faster than structural isomerization, which is irreversible. Both occur much more quickly than photo-oxidation. The photoisomers are less lipophilic than the 4Z,15Z form of bilirubin and can be excreted unchanged in bile without undergoing glucuronidation. Lumirubin isomers can also be excreted in urine. On the other hand, photo-oxidation products are excreted mainly in urine. Once in bile, configurational isomers revert spontaneously to the natural 4Z,15Z form of bilirubin. Overall, photoisomerization rather than photodegradation appears to play a more significant role in bilirubin elimination. Photoisomers products form more rapidly on exposure to phototherapy and appear in blood long before the plasma bilirubin begins to decline. The rate of bilirubin elimination depends on the rates of formation as well as the rates of clearance of these photoproducts.

Over the past 4 decades, a variety of novel strategies have been proposed to enhance the effectiveness of phototherapy (4). Currently, there are limited standardized processes to assess performance of devices or delivery methods for phototherapy. Assessment for efficacy of phototherapy is influenced by: (a) optimization of light administration to achieve a minimum distance between the device and the patient such that the foot print of light covers maximum BSA with minimal physical barriers; (b) infant characteristics such as the severity of jaundice, body surface proportions, tissue dermal thickness, pigmentation, and perfusion; and (c) the duration of treatment to a
specific bilirubin threshold. To better investigate the operation of phototherapy devices in clinical practice, the following technical factors need to be considered.

1. **Use of potent light source**, as defined by its bandwidth and peak emission and its ability to penetrate deeper tissues, is addressed by: (a) use blue lights (at a narrow spectrum with a specific peak wavelength (460 to 500 nm) and a range of emission spectrum (400 to 520 nm) directed at the infant skin; (b) avoidance of concurrent overheating of the infant; (c) minimizing the confounding effect on other biological pigments; (d) diminishing contamination with ultraviolet (UV) lights; and (e) assessing the formation of bilirubin photoisomer by-products that confound total serum bilirubin measurements and may impact bilirubin binding ability to albumin.

2. **The light dose**, as determined by its irradiance or intensity, at which photons are delivered to the body surface per cm² of the exposed skin. The quantitative measure is µW/cm²/nm. To compare spectral irradiance measurements adjusted to specific light wavelength, Vreman, et al.(5) recommend that a calibrated BiliBlanket Meters I and II (Ohmeda, GE Healthcare) yield identical results with stable output of phototherapy light sources. This type of meter was selected from the several devices with different photonic characteristics that are commercially available, because it has a wide sensitivity range (400–520nm with peak sensitivity at 450nm), which overlaps the unconjugated bilirubin absorption spectrum and which renders it suitable for the evaluation of narrow and broad wavelength band light sources. These two devices were found to be exceptionally stable during several years of use, and agreed closely after each annual calibration. Though the device is capable of measuring irradiance with a sensitivity of 0.1 µW/cm²/nm, this level of sensitivity is clinically unnecessary. Increasing the footprint of the light (by increasing the distance) from a single light source can lead to reduced irradiance. Vreman, et al.(5) have also described a unique and optimal technique to assess uniformity of irradiance distribution in the footprint of the light.

3. **Extent of total light exposure**, described as treatable BSA that can be exposed to the device. This may be achieved with the use special blue tubes (BB), by bringing the light source as close to baby as possible. A “spot” halide lamp cannot be used in this manner because of danger due to heat and possible burn. Placing the baby in a bassinet rather than in an incubator provides for an unimpeded exposure to a light source. Alternatively, the light source could be placed within the incubator to avoid exposure through the incubator wall. Performance and integrity of the light sources should be checked for dosage with a equipment-specific radiometer with a recognition that irradiance will vary widely depending on where the measurement is taken. The International Electrotechnical Commission defines the treatment as “effective surface area” of 60×30cm to assess phototherapy devices. However, clinical use and comparison would require an adjustment to a 3-dimensional surface area as well account for infants of varying BSA proportions. Planar (anterior or, posterior) exposure accounts for about 35% of the BSA. In preterms, the head is disproportionately larger and the patched area can be more extensive. Thus, while ensuring protection for the retina and male gonads and diaper protection for hygiene, a maximal area that could receive consistent irradiance is about 80% of the total BSA (circumferential phototherapy).

An insight to the clinical goal, reduction in duration of phototherapy (in hours), is characterized by an evident reversal in rate of rise in total serum (a reduction of >2 mg/dL within 4 to 6 hours of its initiation, about 0.5mg/dL/hr). Response depends on the rate of bilirubin production as well as the effective dosage of light source. In a study reported in this issue of *Indian Pediatrics*, Sivanandan, et al. (6) investigate the previously reported claims of slings made of white reflective material in increasing efficacy of a single-surface compact fluorescent light phototherapy. Through a systematic clinical study design, they were unable to verify a reduction in the duration of phototherapy on addition of slings to phototherapy units. The marginally higher measured irradiance of phototherapy with use of sling was not clinically relevant. Absence of a remarkable therapeutic advantage concurrent with potential risks of shielding the infant from direct
visual observation as well as the hygienic impediments of the shields precludes the use of opaque reflective materials. Although apparently safe for the term infant and larger preterm infants, the application of higher irradiance to the much smaller, more translucent, and less mature preterm infant, who generally is subjected to longer periods of phototherapy, has never been studied systematically. The risks of phototherapy when applied to thin, translucent, antioxidant-insufficient infants have yet to be delineated for a prudent duration of exposure.

In the meantime, our search for evidence-based low cost strategies for safe and effective phototherapy and enhanced “drug delivery” system continues.

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REFERENCES

Hepatitis A – Do we Still Need New Vaccines?

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Hepatitis A is an acute, usually self-limiting disease of the liver caused by hepatitis A virus (HAV), which is primarily transmitted by the fecal-oral route. In young children, HAV infection is usually asymptomatic; whereas symptomatic disease occurs more commonly among adults(1).

An estimated 1.5 million clinical cases of hepatitis A occur each year, majority of which are reported from developing countries. Hepatitis A vaccine in most developing countries is recommended only for travellers to endemic areas. This is the reason why the immunization coverage for hepatitis A is relatively low and the risk of hepatitis A infection is not perceived as a serious health problem(2). However, recently a substantial number of hepatitis A cases have been reported from developed countries. The ongoing outbreak of hepatitis A in the Czech Republic, a country with a very low incidence (2 per 100,000 population) and having a consistent decline in number of cases since the last outbreak in 1979-1980, clearly illustrates this scenario. A very low seroprevalence of HAV facilitated its spread, and hundreds of new cases in a short time led to an escalated demand of the HAV vaccine. The current outbreak was imported from the Mediterranean region highlighting an important