FIG. 1

(57) Abstract: A hyperbilirubinemia phototherapy apparatus (10) includes a phototherapy device (12) including illuminators (20) arranged to illuminate a neonate with phototherapy illumination effective to treat hyperbilirubinemia. A urine collector (14) is configured to collect urine excreted by a neonate while being illuminated with phototherapy illumination by the phototherapy device. A sensing device (28) is secured to at least one of the phototherapy device and the urine collector. The sensing device is configured to output a measurement of a target biomarker in urine collected by the urine collector.
Phototherapy Apparatus With Integrated Urine Collector And Sensor Enabling Reduction Of Side-Effects

FIELD

The following relates generally to measuring and treating hyperbilirubinemia and related conditions. It finds particular application in conjunction with a phototherapy apparatus for treating hyperbilirubinemia in a neonate, and is described with particular reference thereto. However, it is to be understood that it also finds application in other usage scenarios and is not necessarily limited to the aforementioned application.

BACKGROUND

Neonatal hyperbilirubinemia is a condition for which neonatal jaundice is a common symptom. The condition results from insufficient removal of bilirubin from the blood. Bilirubin is a waste product produced during the breakdown of red blood cells, and is ordinarily removed by the liver. In the case of a fetus, the mother’s liver supplements or performs this task, and neonatal hyperbilirubinemia arises when the neonate’s liver is delayed in taking up this task. Neonatal hyperbilirubinemia is commonly present for the first 4-5 days after birth, but can last longer in premature infants, and becomes a serious problem if the total (blood) serum bilirubin (TSB) becomes elevated to the point where it builds up to toxic levels, especially in brain tissue (a condition known as kernicterus).

Phototherapy is a common treatment for neonatal hyperbilirubinemia. Light preferably in the 460-490 nm wavelength range illuminating the skin operates to convert the bilirubin to a form that is less lipophilic and hydrophobic and therefore can be excreted via the urine (and feces) without processing by the liver. Various commercial phototherapy devices are available. As another example, a phototherapy blanket in which LEDs are embedded in an infant-conformal blanket is disclosed in Asvadi et al., Int’l. Pub. WO 2007/091188 A2.

The following provides new and improved methods and systems which overcome the above-referenced problems and others.
BRIEF SUMMARY

Phototherapy for treating hyperbilirubinemia employs illumination in the blue end of the visible spectrum, and is generally considered to have negligible detrimental side effects. Accordingly, monitoring of hyperbilirubinemia phototherapy has typically entailed measuring TSB level 4-6 hours after commencement of treatment to determine efficacy and thereafter every 12 hours until the TSB level reaches an acceptably low level to terminate the phototherapy. Such TSB measurements are commonly measured via drawn blood samples.

However, some possible detrimental side effects of phototherapy have been recognized, such as the possibility of thermal effects, water loss, electrolyte disturbance, bronze baby syndrome, circadian rhythm disorder, and potential longer-term side effects such as melanocytic nevi, skin cancer, allergic diseases, patent ductus arteriosus, and so forth. Phototherapy may also lead to increased oxidative stress due to production of reactive oxygen species and the reduction of bilirubin (which is a potent antioxidant).

To mitigate these side effects, hyperbilirubinemia phototherapy apparatuses and methods are disclosed herein which provide more frequent, and noninvasive, monitoring of one or more target biomarkers in urine. In one illustrative embodiment, a phototherapy blanket is provided with a urine reservoir (e.g. a diaper or other urine-absorbent area) and one or more built-in biomarker sensors are arranged to detect target biomarkers indicative of undesirable side effects and/or characterizing the liver function of the neonate with respect to bilirubin elimination (and hence indicative of the need to continue the phototherapy). Since a neonate typically urinates every 4-6 hours followed by diaper change-out, this approach provides noninvasive monitoring, and provides monitoring at a higher frequency than conventional TSB blood testing every 12 hours without creating an extra burden for the neonate and/or the caregiver.

In some embodiments, a target urine biomarker class is isoprostanes, which provide a measure of lipid peroxidation related to phototherapy breakdown of bilirubin. This can be monitored by an immunoassay that exhibits an observable color change, which can be detected visually by the caregiver or by optical sensor(s). Another suitable biomarker is urobilin, whose presence in urine is indicative of normal bilirubin removal by the liver. Urobilin colorizes urine and can be automatically detected using suitable optical sensor(s).

In accordance with one illustrative example, a hyperbilirubinemia phototherapy apparatus includes a phototherapy device including illuminators arranged to
illuminate a neonate with phototherapy illumination effective to treat hyperbilirubinemia. A urine collector is configured to collect urine excreted by a neonate while being illuminated with phototherapy illumination by the phototherapy device. A sensing device is secured to at least one of the phototherapy device and the urine collector. The sensing device is configured to output a measurement of a target biomarker in urine collected by the urine collector.

In accordance with another illustrative example, a hyperbilirubinemia phototherapy apparatus includes a phototherapy device with illuminators arranged to illuminate a neonate with phototherapy illumination effective to treat hyperbilirubinemia. A sensing device is secured to the phototherapy device and configured to output a measurement of a target biomarker in urine excreted by a neonate receiving phototherapy illumination from the phototherapy device.

In accordance with another illustrative example, a hyperbilirubinemia phototherapy method includes administering hyperbilirubinemia phototherapy to a subject using a hyperbilirubinemia phototherapy device. During the administration of hyperbilirubinemia phototherapy, a sensing device is used to measure a target biomarker in urine excreted by the subject.

One advantage resides in providing more timely monitoring of the need of continued phototherapy and/or side effects of phototherapy treatment of hyperbilirubinemia. Another advantage resides in providing a phototherapy device with a data-driven therapy setting recommendation component.

Still further advantages of the present invention will be appreciated to those of ordinary skill in the art upon reading and understand the following detailed description. It will be appreciated that a given embodiment may provide none, one, two, or more of these advantages.

**BRIEF DESCRIPTION OF THE DRAWINGS**

The invention may take form in various components and arrangements of components, and in various steps and arrangements of steps. The drawings are only for purposes of illustrating the preferred embodiments and are not to be construed as limiting the invention.

FIGURE 1 diagrammatically illustrates a hyperbilirubinemia phototherapy apparatus for administering hyperbilirubinemia phototherapy to a neonate.
FIGURE 2 diagrammatically illustrates a suitable embodiment of the sensing device of the hyperbilirubinemia phototherapy apparatus of FIGURE 1.

FIGURE 3 presents an exemplary flow chart of a hyperbilirubinemia phototherapy method suitably performed using the apparatus of FIGURE 1.

DETAILED DESCRIPTION

With reference to FIGURE 1, a hyperbilirubinemia phototherapy apparatus includes a phototherapy blanket 12 and a urine collector 14 that are each disposed on, or adjacent to, a neonate (or other person) P. The phototherapy blanket 12 at least partially encases the neonate P, and is preferably made of cloth or a textile chosen to provide desirable properties such as conformability to the body or enclosing comfort to the neonate P. As described herein, the phototherapy apparatus provides phototherapy and additionally measures at least one target biomarker in urine excreted by the neonate P. The target biomarker is indicative of the neonate’s liver function (i.e. normal bilirubin elimination) and/or is indicative of an adverse side effect of the phototherapy. In some embodiments, the at least one target biomarker includes at least one of isoprostan concentration in urine, and urobilin concentration in urine. Isoprostan concentration in urine is indicative of lipid peroxidation which may increase due to a combination of production of reactive oxygen species and reduction of bilirubin due to the phototherapy – this increase in lipid peroxidation is a possible undesirable side-effect of the hyperbilirubinemia phototherapy, and hence if the isoprostan concentration increases above some chosen threshold value this may be a basis for recommending reduction in the intensity or spatial extent of the phototherapy illumination, or for turning off the phototherapy illumination entirely. Urobilin accumulates in urine as a product of the normal breakdown of bilirubin, and hence a high urobilin concentration in urine indicates a liver that functions or is starting to function normally, while a low urobilin concentration in urine indicates continued liver deficiency in processing bilirubin and therefore (a probable) continued need for phototherapy.

With continuing reference to FIGURE 1, the phototherapy device further includes an electronic processing device comprising a microprocessor or microcontroller programmed to control the hyperbilirubinemia phototherapy delivered by at least one illumination device 20 of the phototherapy blanket 12. In the illustrative example, the electronic processing device 16 is a phototherapy blanket controller. In the illustrative
embodiment, the illuminators 20 are arranged on or in the phototherapy blanket 12 to illuminate the at least partially encased neonate P with phototherapy illumination effective to treat hyperbilirubinemia. Note that the illuminators 20 are arranged between an outer and inner surface of the blanket 12 so that the phototherapy light is emitted from a side of the blanket facing the neonate P, and accordingly the illuminators 20 are occluded from view by the blanket 12 and accordingly are shown using dashed lines to indicate the illuminators 20 are hidden features in the perspective view of FIGURE 1.

According to guidance from the American Academy of Pediatrics (AAP), phototherapy illumination recommended as effective to treat hyperbilirubinemia has emission in the blue-to-green spectrum, typically 460-490 nm. It will be appreciated that illumination having a wavelength range spanning only a portion of this range (e.g. 450-470 nm), or even emitting at a single wavelength in this range, and/or extending outside of this range (e.g. 465-520 nm), should also be effective. The AAP guidance further recommends irradiance of at least 30 microwatts/cm²/nm (for example, measured using an irradiance meter calibrated over the chosen wavelength range). It will again be appreciated that this is recommended guidance and that a lower irradiance may still provide therapeutic benefit, while higher irradiance is likely to provide increasing benefit, i.e. increasing rate of bilirubin breakdown albeit possibly with increased undesirable side-effects. The AAP guidance further recommends illuminating the neonate over a large a portion of the body surface as possible, and indicates that TSB reduction should be observed during the first 4 to 6 hours of exposure if the phototherapy is effective.

In one suitable embodiment, the illuminators 20 are light emitting diodes (LEDs) arranged on or in the phototherapy blanket 12 and configured to emit light in the wavelength range 460-490 nm. In one suitable assembly, the LEDs are mounted on textile ribbons with conductive wires attached in roughly parallel rows on the inner side of the outer surface of the phototherapy blanket 12 that is, on the side facing the neonate P. The ribbons provide a convenient way to mount the LEDs and to route electrical power to the LEDs, but alternative assemblies are contemplated, such as mounting LEDs on flexible circuit board strips or tabs sewn onto the blanket with discrete wires running through the fabric of the phototherapy blanket 12. The phototherapy blanket may be a multi-layer blanket, for example with a spacer layer to maintain a distance between the LEDs and the skin of the neonate P (with apertures for the LEDs), and an inner liner to protect the neonate from contact with the
illuminators and their wiring or circuit boards (such a liner may prevent touching of the LEDs through the apertures and ingestion of dirt and fluids into the blanket, or may be thin enough and sufficiently translucent in the therapeutic wavelength range, e.g. 460-490 nm, to permit effective phototherapy). In other embodiments, the blanket 12 can include other types of light sources (e.g., vertical-cavity surface-emitting lasers (VCSELs) or light from an external source that may be guided to the blanket with optical fibers. Some suitable phototherapy blanket embodiments are described, by way of illustration, in Asvadi et al., Int’l. Pub. WO 2007/091188 A2.

The phototherapy blanket controller 16 preferably controls the illuminators 20 in order to control the therapeutic illumination output by the illuminators 20. This control can be open-loop, e.g. the phototherapy blanket controller 16 may apply a fixed electrical current to the electrical circuit driving the illuminators 20, or the control may be closed-loop using a feedback signal provided by one or more photodetectors (not shown) also arranged on or in the phototherapy blanket 12. The illustrative controller 16 further includes a display component 22 via which the user (e.g. nurse, physician, parent, or so forth) is informed of the current phototherapy setting(s) or other settings (connection to terminals, battery status, and the like), and which has one or more user input buttons or the like 24 via which the user can set up the phototherapy or optionally perform other user interfacing operations.

Advantageously, the illustrative phototherapy device 12 having a blanket form at least partially encasing the neonate P provides illumination of the neonate P over most of the neonate’s external surface area (thus maximizing effectiveness of the hyperbilirubinemia phototherapy according to the AAP guidance) while still providing for the neonate P to be clothed (in the phototherapy blanket 12) and advantageously reducing or eliminating exposure of the neonate’s eyes to the therapeutic illumination. In some embodiments, the controller 16 can be set to power only a sub-set of the illuminators 20, for example only the illuminators on the front side of the neonate P (or, alternatively, only on the back side of the neonate, or alternatively every other strip may be turned off, et cetera). This provides for adjustment of the spatial distribution of the phototherapy illumination which in some cases may be a preferable way to control the hyperbilirubinemia phototherapy as compared with adjusting the illumination intensity (or both intensity and spatial area may be adjusted).

While the illustrative embodiment employs a hyperbilirubinemia phototherapy device in the form of the illustrative phototherapy blanket 12 including LED illuminators 20,
the disclosed approaches are also compatible with other types of hyperbilirubinemia phototherapy devices, such as an incubator with compact fluorescent lighting emitting at a therapeutic wavelength (e.g. in the 460-490 nm range) or a compact fluorescent or incandescent lamp arranged to similarly illuminate the neonate. These alternative approaches can be effective, but may have certain disadvantages such as illuminating the neonate over a smaller fraction of its total surface area, producing stray illumination into the neonate’s eyes, requiring more electrical power, and requiring the neonate be naked so as to be exposed to the therapeutic illumination.

The urine collector 14 is positioned around the waist and/or buttocks of the neonate P so as to cover the genitalia (i.e. to collect urine). In some embodiments, the urine collector 14 is a conventional diaper; in other embodiments it is a diaper-like structure or absorbent pad; more generally, the urine collector 14 can have any configuration suitable for collecting (e.g. absorbing) urine. It is contemplated for the urine collector 14 to have different configurations for male versus female neonates. In an economical embodiment, the urine collector 14 is a disposable item, i.e. a diaper or other consumable, which is separate from the phototherapy blanket 12 which is arranged to surround the urine collector 14 (although as shown in FIGURE 1 the illuminators 20 typically do not overlap the urine collector 14 since the latter would block or absorb the therapeutic illumination, or, in some embodiments, the urine collector can include one or more non-transparent parts, such as an absorbing unit). Alternatively, the urine collector 14 can be detachably attached to the phototherapy blanket 12, for example using Velcro™. The neonate P typically will urinate every 4-6 hours, and it is generally expected that a nurse, parent, or other caretaker will change out the urine collector 14 after each urination event.

With continuing reference to FIGURE 1 and with further reference to FIGURE 2, as disclosed herein the hyperbilirubinemia phototherapy apparatus 10 provides feedback regarding liver function and/or side effects of the hyperbilirubinemia phototherapy via measurement of at least one target biomarker in urine excreted by the neonate P. To this end, at least one sensing device 28 is secured to the phototherapy blanket 12 and/or to the urine collector 14 and is configured to output a measurement of a target biomarker in urine collected by the urine collector 14. In some embodiments, the sensing device 28 includes an immunoassay 30 (FIGURE 2), for example comprising an antibody that is embedded in or coated onto the urine collector, or a lateral flow assembly (not shown in FIGURE 2) and that
exhibits a color change or a change in fluorescence in response to the concentration of a target biomarker to be detected in the collected urine exceeding some color transition threshold. Such a color change can be detected visually, e.g. observed by the nurse, parent, or other caregiver when changing out the diaper or other urine collector 14. Additionally or alternatively, as seen in FIGURE 2 the sensing device 28 can include an optical detection sub-system for automatically detecting the color or fluorescence change. For example, in illustrative FIGURE 2 the sensing device 28 further includes a light source 32 secured to the phototherapy blanket 12 and at least one scattered light detector 34 or fluorescence detector 36 secured to the phototherapy blanket 12, and/or a forward scattered light detector 38 secured to the urine collector 14 so as to detect light from the light source 32 that scatters through the urine collector 14 dependent on the color change of the urine sample. Advantageously, the use of an optical detection system 32, 34, 36, 38 can provide more finely resolved data, e.g. not simply a binary “color change” or “no color change” assessment, but a quantitative measure of how much the color has changed, which can be a better method of judging whether the color change threshold has been passed.

Rather than embedding or coating the immunoassay 30 in or on the urine collector 14, it is alternatively contemplated for the immunoassay to be a separate component, e.g. a cover sheet containing the immunoassay which is disposed over (and in intimate contact with) the urine collector. Some suitable target biomarkers, such as urobilin, produce a color change in the urine without the use of an immunoassay, and if such a biomarker is employed then the immunoassay may be omitted.

Various hyperbilirubinemia markers in urine can be detected in order to assess the liver function and/or in order to assess undesired side effects that may be generated by the hyperbilirubinemia phototherapy. Some examples are given below.

In one approach, the detected target biomarker is isoprostane concentration in urine. This biomarker is related to the possible undesirable side effect of increased oxidative stress as follows. Phototherapy leads to the production of reactive oxygen species and the reduction of bilirubin, which is a potent antioxidant. The result can be an increased oxidative stress for the body of the infant, leading to lipid peroxidation. Isoprostanes in urine are a measure for lipid peroxidation. Isoprostanes can be suitably detected with the immunoassay 30 (biochemical test for detection of macromolecules based on coupling to antibodies and labelling) designed to produce a visibly detectable color change observable by the caretaker
as a function of isoprostanol concentration, and/or the color change may be detected with the optical sensor 34, 36, 38. Rather than detecting a color change, the immunoassay 30 may be designed to produce a detectable fluorescence as the label, which is suitably produced in response to illumination by the light source 32 and detected by the fluorescence detector 36. Although FIGURE 2 shows that the optical sensor 34 is adjacent to the light source 32, it will be appreciated that the fluorescence detector 36 can be positioned adjacent to the light source.

In another approach, the detected target biomarker is urobilin, whose concentration in urine is related to the need of continued phototherapy as follows. When the neonate’s liver starts to work normally it will remove (unconjugated) bilirubin from the blood eventually resulting in urobilin in the urine. As bilirubine is not soluble in water, it is coupled to albumine in the blood. A functioning liver takes it up and couples it to glucuron (by the enzyme glucuronyltransferase). Once coupled to glucuron, the bilirubine can be excreted in the bile. Via the gall bladder the conjugated bilirubine is excreted in the intestines. In the intestines the bilirubine is converted to urobinolinogene. Urobinolinogene is oxidized either in the intestines (to stercobiline) or taken up in the blood and then oxidized to urobilin in the kidneys. Urobilin gives the color to urine. The color of the urine in the urine collector 14 may be a direct indication of the liver function (in which case the immunoassay 30 is omitted), or the immunoassay 30 is provided for more accurate detection. A resulting color change or fluorescence is detected by the optical detection system 32, 34, 36, 38.

Alternatively, urobilin can be detected via absorption spectrum analysis using the light source 32 and detector 38. It will be appreciated that other biomarkers may detect efficacy of the phototherapy, such as a decrease of TSB.

Each of the optical components 32, 34, 36, 38 of the sensing device 28, if provided, may be secured to the phototherapy blanket 12 and/or to the urine collector 14. Because the urine collector 14 becomes soiled each time the neonate P urinates (which occurs every 4-6 hours typically), the urine collector 14 is preferably a disposable item. As such, it may be more cost-effective to secure most or all of the optical components 32, 34, 36 to the phototherapy blanket 12 so that they are not replaced with each urine collector change-out. Alternatively, the urine collector may be washable/reusable, but in this case any attached optical components would need to be robust against the washing cycle. Optical components 32, 34, 36 which are mounted to the phototherapy blanket 12 should be positioned so as to interact appropriately with the urine collector 14, e.g. the light source 32 should be arranged
to apply light to the urine collector 14 in a region likely to have a large quantity of collected urine, and the optical sensors 34, 36 should be positioned to detect that light after scattering or to detect induced fluorescence or other optical output generated by the label of the immunoassay 30. In general, the optical detection can detect the labeled target biomarker by detecting forward-scatter of the cells, side scatter of the cells, fluorescent emission of the cells, or so forth. The relative amount of optical power on the detector 34, 36, 38 is measured. The light source 32 emits light in a wavelength range effective to activate the immunoassay label. In some embodiments, the excitation wavelength is in the ultraviolet to blue range (200-490 nm), e.g. between 200-290 nm or between 450-490 nm. For example, the light source 32 can be a collimated LED source, or alternatively, a laser source for small collimation angle and specific spectral excitation. Measuring fluorescence, side scattering and forward scattering in a flowing fluid is known as Laser Flow Cytometry. It will be noted that the latter wavelength range overlaps the AAP-recommended therapeutic wavelength range of 460-490 nm for hyperbilirubinemia phototherapy – if this is the case for the deployed immunoassay 30, then it is contemplated to employ the illuminators 20 as the light source for optically activating the immunoassay label (so that the separate activation light source 32 is optionally omitted).

During operation, the sensing device 28 measures at least one target biomarker in urine collected by the urine collector 14. If the sensing device 28 is an immunoassay that exhibits a color change intended to be detected visually by the caregiver during change-out of the urine collector 14, then the optical components 32, 34, 36, 38 are suitably omitted and detection of the target biomarker is performed manually by visual inspection of the urine collector 14.

With returning reference to FIGURE 1, if on the other hand optical sensing components 32, 34, 36, 38 are employed, these are preferably connected with the phototherapy blanket controller 16 (or some other electronic data processing device) by suitable wiring 40 or by a wireless connection, and the controller 16 (or more particularly an electronic processor of the controller) is programmed to generate a hyperbilirubinemia phototherapy recommendation, for example selected from a group consisting of: (i) a recommendation to perform a TSB test; (ii) a recommendation to continue phototherapy illumination, (iii) a recommendation to adjust intensity of the phototherapy illumination, (iv)
a recommendation to adjust spatial distribution of the phototherapy illumination, and (v) a recommendation to turn off the phototherapy illumination.

In some embodiments, a TSB test is to be performed by the caregiver. Based on the outcome of this test, the physician responsible for the neonate decides whether to reduce or discontinue the phototherapy. The provided information on the concentration of biomarkers for side-effects or normal liver function can be taken into account in this decision. It will be appreciated that the TSB test provides a confirmation as to whether to reduce or discontinue phototherapy, as a TSB test is considered the “gold standard” in determining whether to apply phototherapy. However, measurement of the target biomarkers (e.g., isoprostan, urobilin, and the like) can also be used to determine whether to begin/reduce/discontinue phototherapy.

As another example, if the target biomarker is isoprostan concentration in urine, then the controller 16 is programmed to generate a recommendation to reduce intensity (i.e. average spectral irradiance) or spatial distribution (i.e. body coverage is reduced while the spectral irradiance in the illuminated parts remains the same) of the phototherapy illumination or to turn off the phototherapy illumination entirely if the measurement of isoprostan concentration in urine is greater than a threshold. Such recommendations are motivated by high isoprostan concentration being indicative of the neonate P experiencing increased oxidative stress due to the hyperbilirubinemia phototherapy.

As yet another example, if the target biomarker is urobilin concentration in urine, then the controller 16 is programmed to generate a recommendation to generate a hyperbilirubinemia phototherapy recommendation indicating starting or normal liver functionality (independent of phototherapy) of the neonate being treated by the phototherapy device 12, or, alternatively, a reduction of intensity or spatial coverage, or turning of the illuminators 20. In this example, a higher urobilin concentration in urine is indicative of normal elimination of bilirubin by the liver of the neonate. Therefore phototherapy may be reduced or discontinued.

The hyperbilirubinemia phototherapy recommendation may be used in various ways. In one approach, the controller 16 directly controls the phototherapy device (e.g. the illuminators 20 of the phototherapy blanket 12 in the illustrative embodiment) to implement the hyperbilirubinemia phototherapy recommendation, e.g. by switching off some or all of the illuminators 20, and/or reducing their drive current, in response to the isoprostan
concentration in urine exceeding some threshold value chosen as indicative of excessive oxidative stress.

However, directly controlling the phototherapy on the basis of the generated hyperbilirubinemia phototherapy recommendation may be problematic. Such control may contravene therapy prescribed by the neonate’s physician. Additionally, target biomarkers in the urine are generally considered less reliable than the “gold standard” of total serum bilirubin (TSB) measured via a blood test.

Accordingly, in some embodiments the hyperbilirubinemia phototherapy recommendation is not directly implemented by the phototherapy controller 16, but rather is communicated to the nurse or caregiver, for example via the display component 22 of the controller 16. Additionally or alternatively, the controller 16 may be provided with a flashing light, audio alarm or the like which may be activated based on the hyperbilirubinemia phototherapy recommendation. Additionally or alternatively, the hyperbilirubinemia phototherapy recommendation may be communicated to a neonatal ward nurses’ station or the like via a wired or wireless communication pathway.

The measurement of the monitored target biomarker in urine generated by the sensing device 28 is valid only when the urine collector 14 has collected a sufficient quantity of urine. Typically, a neonate urinates every four to six hours, and the urine collector 14 is changed out shortly thereafter. Accordingly, the measurement output by the sensing device 28 is valid for the time interval between the urination event and the change-out. Typically, the output of the optical detector 34, 36, 38 will have a readily identified “no signal” output in the time interval before urine is collected. For example, the luminescence detector 36 will output a low or null signal until the biomarker-containing urine is excreted, while a transmission detector may have a high signal until a light-absorbing biomarker in urine is present. The optical detection system may measure at different wavelengths of emission of the light source 32 or different wavelengths of sensitivity of detectors 34, 38, or a combination of color and fluorescence measurements to detect presence of urine on the one hand (independent of biomarker concentration) and biomarker quantity on the other hand.

With reference to FIGURE 3, a suitable processing sequence in view of the foregoing is described. In an operation 50, the sensing device 28 continually generates measurements, which are checked for validity. Until the neonate P urinates, these validity checks will indicate invalid measurements. When a valid measurement is detected at
operation 50, thus indicating the neonate P has urinated and the urine has collected in the
urine collector 14, processing flows to an operation 52 which compares the measurement
with a threshold, and then to an operation 54 at which the hyperbilirubinemia phototherapy
recommendation is generated based on this threshold. In an operation 56, the
hyperbilirubinemia phototherapy recommendation is displayed (or alternatively the
phototherapy apparatus is directly controlled to implement the hyperbilirubinemia
phototherapy recommendation).

In the illustrative examples, the subject is a neonate P having neonatal
hyperbilirubinemia. However, hyperbilirubinemia can also afflict adults, e.g. elderly patients
with a jaundice condition, Crigler-Najjar syndrome, and the like, and the disclosed
hyperbilirubinemia phototherapy apparatuses and methods are readily adapted for such an
adult patient (e.g. by substituting an adult-sized phototherapy blanket for the illustrative
neonatal therapy blanket 12).

The invention has been described with reference to the preferred embodiments.
Modifications and alterations may occur to others upon reading and understanding the
preceding detailed description. It is intended that the invention be constructed as including
all such modifications and alterations insofar as they come within the scope of the appended
claims or the equivalents thereof.
CLAIMS

1. A hyperbilirubinemia phototherapy apparatus (10) comprising:
   a phototherapy device (12) including illuminators (20) arranged to illuminate a
   neonate with phototherapy illumination effective to treat hyperbilirubinemia;
   a urine collector (14) configured to collect urine excreted by a neonate while being
   illuminated with phototherapy illumination by the phototherapy device; and
   a sensing device (28) secured to at least one of the phototherapy device and the urine
   collector, the sensing device configured to output a measurement of a target biomarker in
   urine collected by the urine collector.

2. The hyperbilirubinemia phototherapy apparatus of claim 1 wherein:
   the phototherapy device comprises a phototherapy blanket (12) configured to at least
   partially encase a neonate, the phototherapy blanket including the illuminators (20) arranged
   on or in the phototherapy blanket to illuminate the at least partially encased neonate with
   phototherapy illumination effective to treat hyperbilirubinemia; and
   the urine collector (14) is configured to collect urine excreted by a neonate while at
   least partially encased in the phototherapy blanket.

3. The hyperbilirubinemia phototherapy apparatus of claim 2 wherein the sensing
   device (28) includes:
   a light source (32) secured to the phototherapy blanket (12) or the urine collector (14)
   and configured to emit light onto the urine collector; and
   a light detector (34, 36, 38) secured to the phototherapy blanket (12) or the urine
   collector (14) and configured to detect at least one of scattered, reflected, transmitted, and
   fluorescent light emanating from the urine collector responsive to light emitted onto the urine
   collector by the light source.

4. The hyperbilirubinemia phototherapy apparatus of any one of claims 1-3 wherein
   the illuminators (20) comprise light emitting diodes (LEDs) arranged on or in the
   phototherapy blanket (12) and configured to emit light in the wavelength range 460-490 nm.
5. The hyperbilirubinemia phototherapy apparatus of any one of claims 1-4 further comprising:

a monitoring device (16) comprising an electronic processor programmed to generate a hyperbilirubinemia phototherapy recommendation based on a measurement of the target biomarker output by the sensing device (28) and at least one of (1) display the hyperbilirubinemia phototherapy recommendation on a display component (22) of the monitoring device and (2) control the illuminators (20) of the phototherapy device (12) to implement the hyperbilirubinemia phototherapy recommendation.

6. The hyperbilirubinemia phototherapy apparatus of claim 5 wherein the monitoring device (16) is programmed to generate the hyperbilirubinemia phototherapy recommendation selected from a group consisting of: (i) a recommendation to perform a TSB test; (ii) a recommendation to continue phototherapy illumination, (iii) a recommendation to adjust intensity of the phototherapy illumination, (iv) a recommendation to adjust spatial distribution of the phototherapy illumination, and (v) a recommendation to turn off the phototherapy illumination.

7. The hyperbilirubinemia phototherapy apparatus of claim 6 wherein the sensing device (28) is configured to output a measurement of isoprostane concentration in urine collected by the urine collector (14) and the monitoring device (16) is programmed to generate a recommendation to reduce intensity or spatial distribution of the phototherapy illumination or to turn off the phototherapy illumination if the measurement of isoprostane concentration in urine is greater than a threshold.

8. The hyperbilirubinemia phototherapy apparatus of claim 6 wherein the sensing device (28) is configured to output a measurement of urobilin concentration in urine collected by the urine collector (14) and the monitoring device (16) is programmed to generate a hyperbilirubinemia phototherapy recommendation indicating normal liver functionality of the neonate being treated by the phototherapy device (12) based on the measurement of urobilin concentration in urine collected by the urine collector.
9. The hyperbilirubinemia phototherapy apparatus of any one of claims 5-8 wherein the monitoring device (16) is a controller of the phototherapy device (12) and is attached to the phototherapy device directly or by an electrical cord (40).

10. The hyperbilirubinemia phototherapy apparatus of any one of claims 1-9 wherein the sensing device (28) includes at least one immunoassay configured to output a signal indicative of a target biomarker concentration in urine collected by the urine collector (14), the signal including a change in urine color based on the target biomarker concentration.

11. The hyperbilirubinemia phototherapy apparatus of any one of claims 1-10 wherein the sensing device (28) is configured to output a measurement of a target biomarker comprising at least one of isoprostane concentration in urine collected by the urine collector (14) and urobilin concentration in urine collected by the urine collector.

12. A hyperbilirubinemia phototherapy apparatus (10) comprising:

a phototherapy device (12) including illuminators (20) arranged to illuminate a neonate with phototherapy illumination effective to treat hyperbilirubinemia; and

a sensing device (28) secured to the phototherapy device and configured to output a measurement of a target biomarker in urine excreted by a neonate receiving phototherapy illumination from the phototherapy device.

13. The hyperbilirubinemia phototherapy apparatus of claim 12 wherein:

the phototherapy device comprises a phototherapy blanket (12) configured to at least partially encase a neonate, the phototherapy blanket including the illuminators (20) arranged on or in the phototherapy blanket to illuminate the at least partially encased neonate with phototherapy illumination effective to treat hyperbilirubinemia.

14. The hyperbilirubinemia phototherapy apparatus of claim 13 wherein the sensing device (28) includes:

a light source (32) secured to the phototherapy blanket (12) and configured to emit light onto a diaper or other urine collector (14); and
a light detector (34, 36, 38) secured to the phototherapy blanket (12) and configured to detect at least one of scattered, reflected, transmitted, and fluorescent light emanating from the diaper or other urine collector responsive to light emitted onto the diaper or other urine collector by the light source.

15. The hyperbilirubinemia phototherapy apparatus of any one of claims 13-14 wherein the illuminators (20) comprise light emitting diodes (LEDs) arranged on or in the phototherapy blanket (12) and configured to emit light in the wavelength range 460-490 nm.

16. The hyperbilirubinemia phototherapy apparatus of any one of claims 13-15 further comprising:
   a phototherapy blanket controller (16) configured to control the illuminators (20) of the phototherapy blanket (12) and to display a hyperbilirubinemia phototherapy recommendation generated by the phototherapy blanket controller from a measurement of the target biomarker output by the sensing device (28).

17. The hyperbilirubinemia phototherapy apparatus of any one of claims 12-17 wherein the sensing device (28) is configured to output a measurement of a target biomarker comprising at least one of isoprostane concentration in urine and urobilin concentration in urine.

18. A hyperbilirubinemia phototherapy method comprising:
   administering hyperbilirubinemia phototherapy to a subject using a hyperbilirubinemia phototherapy device (12); and
   during the administration of hyperbilirubinemia phototherapy using a sensing device (28), measuring a target biomarker in urine excreted by the subject.

19. The hyperbilirubinemia phototherapy method of claim 18 further comprising:
   using an electronic controller (16) of the hyperbilirubinemia phototherapy device (12), generating a hyperbilirubinemia phototherapy recommendation based on the measured target biomarker in urine excreted by the subject; and
   displaying the hyperbilirubinemia phototherapy recommendation on a display component (22) of the electronic controller.
20. The hyperbilirubinemia phototherapy method of any one of claims 18-19 wherein the administration of hyperbilirubinemia phototherapy comprises:

operating light emitting diodes (LEDs) (20) of a phototherapy blanket (12) that at least partially encases a neonate to illuminate the at least partially encased neonate with phototherapy illumination in a wavelength range of 460-490 nm.
Is measurement in valid range?

50

Compare measurement with threshold

52

Generate hyperbilirubinemia phototherapy recommendation based on comparison

54

Display recommendation or directly implement by controlling illuminators

56

FIG. 3
### INTERNATIONAL SEARCH REPORT

**PCT/IB2016/053694**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61N5/06  
ADD. A61B10/00 A61B5/145

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61N  A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Relevant to claim No.</th>
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<td>WO 00/49948 A2 (UNIV ULSTER [GB]; MULHOLLAND CLIVE WILLIAM [GB]; THURNHAM DAVID IAN [G]) 31 August 2000 (2000-08-31) page 1, line 3 - page 2, line 27 page 11, line 29 - page 12, line 19</td>
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**Further documents are listed in the continuation of Box C.**

**See patent family annex.**

* Special categories of cited documents:
  * **A** document defining the general state of the art which is not considered to be of particular relevance
  * **E** earlier application or patent but published on or after the international filing date
  * **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  * **O** document referring to an oral disclosure, use, exhibition or other means
  * **P** document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search 6 September 2016

Date of mailing of the international search report 19/09/2016

Name and mailing address of the ISA/  
European Patent Office, P.B. 5018 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-0040,  
Fax. (+31-70) 340-2016

Authorized officer Lohmann, Stefan

Form PCT/ISA/210 (second sheet) (April 2005)
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INTERNATIONAL SEARCH REPORT

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. claims Nos.: 18-20 because they relate to subject matter not required to be searched by this Authority, namely:
   Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)
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