

Ursodeoxycholic acid use is associated with significant risk of morbidity and mortality in infants with cholestasis

A strobe compliant study

Magd Ahmed Kotb, MD^{a,*}, Dalia Mosallam, MD^a, Christine William Shaker Basanti, MD^a, Sally Talaat Mostafa El Sorogy, MBBCh^b, Ahmed M. Badr, MD^a, Hend El Hosainy Abd El Baky^a, Iman Hassan Draz, MD^a

Abstract

The off-label use of medications is a “right” for pediatricians, owing to lack of enough safety and effectiveness drug trials in pediatric age group. Pediatricians have to rely on their personal judicial use of medications in children.

We studied off-label use of ursodeoxycholic acid (UDCA) retrospectively during 2005 to 2015 among those who attended the Pediatric Hepatology Unit, Cairo University.

We analyzed data of 779 neonates and infants with cholestasis. 15% dropped out. Males comprised 374 (56.5%). Cholestasis was due to surgical causes in 129 (19.5%), neonatal hepatitis in 445 (67.2%), and paucity of intrahepatic bile ducts in 88 (13.3%). Three hundred sixty (54.4%) received UDCA (15–30 mg/kg/d), and 302 (45.6%) did not. Both groups were matched as regards causes and severity of cholestasis. Those who received UDCA had worse outcome ($P < .001$), and more complications ($P < .001$). A total of 73.1% (221) achieved cure without UDCA compared to only 45.8% (165) of those on UDCA ($P < .001$).

UDCA is not effective and not safe in Egyptian neonates and infants with cholestasis. UDCA use compromises chance of cure, and is associated with serious morbidity, progression of disease, and death. UDCA off-label use mortality was absolutely preventable. Off-label use of UDCA in neonates and children should be utterly prohibited. Information of use of off-label medications, effectiveness, and safety, should be recorded, analyzed, and made available within context of Off-label Use Registry Studies with informed consent of parents.

Abbreviations: ALT aspartate = alanine aminotransferase, AST = aspartate aminotransferase, EHBA = extrahepatic biliary atresia, NH = neonatal hepatitis, PIBR = paucity of intrahepatic biliary radicals, UDCA = ursodeoxycholic acid.

Keywords: cholestasis, death, liver cell failure, neonates infants children pediatric, off-label use, UDCA, ursodeoxycholic acid

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This article does not contain any studies with human participants or animals performed by any of the authors. It is a retrospective study including all files of neonates and infants who presented with cholestasis during 2005 to 2015. The study was approved by the Pediatric Department Committee for Post-Graduate Studies and Research, and by Post-Graduate Studies and Research Administration, Faculty of Medicine, Cairo University, Egypt.

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MAK, DM, CWSB, AMB, IHD are holders of Medical doctorate degrees.

^a Pediatrics Department, Faculty of Medicine, Kasr Alainy, Cairo University,

^b Public Mounira Hospital, Cairo, Egypt.

* Correspondence: Magd Ahmed Kotb, Cairo University, New Children Hospital, Cairo University, Kasr Al Ainy Street, Cairo 11562, Egypt. (e-mail: magdkotb@kasralainy.edu.eg).

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Key Points

- Lack of sufficient trials drives physicians to prescribe unlicensed medicines off-label, which results in unseen morbidities, mortalities and consumes resources. Commonest 10 anticancer drugs off-label use in USA cost almost \$5 billion.
- Ursodeoxycholic acid (UDCA) off-label use caused serious morbidity and mortality among Egyptian infants with cholestasis until 2005, enforcing package insert change.
- The study confirms that UDCA is not safe and not effective in infants with cholestasis
- Package insert change did not change prescribing patterns of UDCA.
- Establishment of registry for off-label use is mandatory.

1. Introduction

The off-label use of medications is a “right” for pediatricians who are faced by lack of evidence derived from drug trials in pediatric age, hence they are in a sense forced to take blinded decisions to risk and benefits that are judiciously filled with hope and faith.

Off label is thought of as a bare necessity, that is, important to broaden treatment options.^[1] Yet, experience is the least level of evidence, and history provides a lot of evidence against unregulated, unfounded, and unsupported right of professionals.^[2,3] While off-label use is practiced daily, the valuable information of this use, effects, safety, and outcome is not collected, analyzed, or benefitted from, contrary to outcomes of licensed use which has to be reported. The effectiveness and safety of off label medications used frequently in children are not evidence based. Ursodeoxycholic acid (UDCA) is a bile acid approved in adults for management of cholesterol gallstones and primary biliary cirrhosis. UDCA undergoes metabolism into lithocholic acid that leads to cholestatic liver injury, liver cell failure, and death.^[4,5] UDCA is not licensed for children.^[6]

In a long-term, randomized, double-blind case-controlled trial of high-dose UDCA (28–30 mg/kg/d) in primary sclerosing cholangitis UDCA was shown to cause drop of hepatic transaminases and cause higher rates of serious adverse events including increased risk of death to more than double fold.^[4,5] Likewise, 10 years ago we published our 10-year experience with UDCA in Egyptian infants and neonates with cholestasis (obstructive and nonobstructive), that demonstrated that UDCA reduced chance of cure and its use was associated with serious adverse effects including liver cell failure and death.^[7,8] UDCA use in children is strictly off-label.^[9] We aimed to study pattern of use of UDCA in neonatal cholestasis in response to our initial reports.^[7,8]

2. Material and methods

Archived files of neonates and infants suffering from cholestasis who presented to the Pediatric Hepatology Clinic, New Children Hospital during 2005 to 2015 were analyzed. The study was approved by the Pediatric Department Committee for Post-Graduate Studies and Research, Faculty of Medicine, Cairo University, Egypt. Data were retrieved from archives of files of the Pediatric Hepatology Clinic, New children Hospital, Cairo University.

The diagnosis of extrahepatic biliary atresia was depended upon clinical picture, imaging, biopsy findings, and operative findings. Neonatal hepatitis and paucity of intra-hepatic bile ducts (PIBD) were diagnosed clinically, by imaging, and typical findings upon percutaneous liver biopsy findings and confirmed by specific investigations when appropriate according to clinical situation. Syndromic PIBD, none-syndromic, and vanishing bile duct syndrome diagnosis depended on presence of associated morphologic features, biopsy findings, and not on genetic testing.^[7,8] Records of infants who were followed up for less than 30 days were excluded from the study.

The outcome was graded as: “cured/successful” when subject with cholestasis became anicteric and maintained alanine and aspartate aminotransferase levels within and less than double highest normal level, “improved” when there was persistent jaundice, stable disease, and maintained stable alanine aminotransferase levels within less than 4 times highest normal level and “failed” outcome when the cholestasis remained stationary and/or developed progressive disease, chronic hepatitis, or liver cell failure. Statistical Package for Social Sciences version 19 (SPSS, Chicago, IL) was used to conduct all statistical analyses in this study. Data of medical condition at time of initiation of UDCA intake, and at final visit was included.

3. Results

The Hepatology Unit received 6754 infants and children suffering from liver disease during 2005 to 2015, of them 779 infants suffered from cholestasis. Those who followed up were 662 (85%) while 117 (15%) dropped out with no record of a second visit. Males comprised 374 (56.5%) and 288 (43.5%) were females. Almost a third (34.7%, 230 cases) were products of consanguineous marriages (Fig. 1). Etiology of cholestasis is presented in Table 1. Data shows that among the studied cohort 360 (54.4%) received UDCA (15–30 mg/kg/d), and 302 (45.6%) did not. Both groups were compatible (Table 2). Neonates on UDCA presented to our medical attention on UDCA. Those who received UDCA had worse outcome ($P < .001$), and more complications ($P < .001$) (Fig. 1 and Tables 2 and 3, respectively). Cure was achieved in 221 (73.1%) of those without UDCA compared to only 165 (45.8%) of those on UDCA ($P < .001$) despite comparable severity and aetiology of disease. Chance of cure decreased to less than third (0.31) with intake of UDCA ($P < .000$) (95% confidence interval 0.223–0.431). There was no decline in use of UDCA over time since 2005 (Fig. 2).

4. Discussion

Case-control studies for children medications are greatly needed. Intervention adult studies are not enough evidence to support use in children. UDCA is neither effective nor safe in neonatal cholestasis ($P < .001$). Those who received UDCA and those who did not were matched as regards as underlying disease, severity of disease, complications, and functional decompensation of liver condition at time of presentation. Hence, the poor outcome of those on UDCA cannot be explained by any of these factors. The number of cases in this study is big enough to draw rather solid conclusion about UDCA ineffectiveness and lack of safety in neonates and infants.

4.1. Evidence is against UDCA use in neonatal cholestasis

UDCA is neither effective nor safe among our studied cohort of Egyptian neonates and infants with cholestasis ($P < .001$). This is consistent with the previously published outcomes of UDCA in the previous decade.^[7,8] The dose prescribed to those on UDCA (15–30 mg/kg/d) was a high dose that was noted to cause liver cell failure and death in adults with primary sclerosing cholangitis.^[4,5] The lack of evidence derived from randomized double blind case-control studies led to the use of this alarming empirical high toxic dose among our studied cohort.^[9] It was prescribed upon pediatrician “opinion.”

4.2. UDCA is not effective and not safe in neonatal cholestasis

UDCA withdrawal is associated with deterioration of liver condition among adults, despite drop of levels of lithocholic acid that is responsible for grave morbidity and mortality. The UDCA withdrawal syndrome does not occur in patients who responded by absolute improvement in their quality of life or cure of liver condition upon receiving UDCA. The notorious UDCA withdrawal syndrome is observed in withdrawal of steroids as well, is seen by some as evidence that UDCA administration might be “good.”^[10,11]

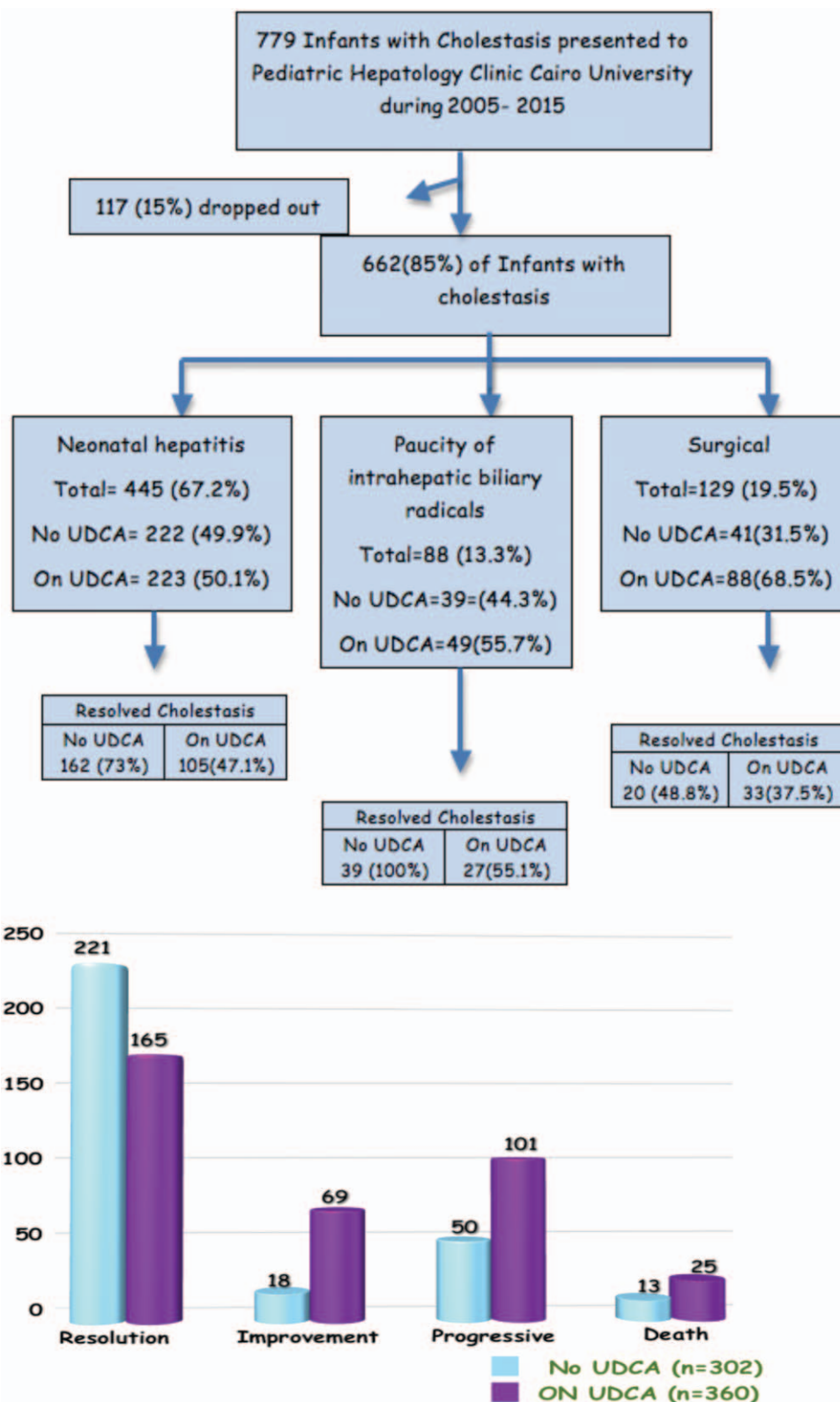


Figure 1. Flow chart of neonates and infants with cholestasis who attended Pediatric Hepatology Clinic, Cairo University during 2005 to 2015 and the outcome of their Cholestasis according to UDCA intake. UDCA=ursodeoxycholic acid.

Table 1
Aetiology and characteristics of cohort that received UDCA.

	Cases who did not receive UDCA N = 302 (45.6%)		Cases on UDCA N = 360 (54.4%)		P
	Mean	SD	Mean	SD	
Age at onset (mean in mo)	0.57	0.22	0.56	0.21	.2
	Number	%	Number	%	
Gender					
Females	123	40.7	165	45.8	.2
Males	179	59.3	195	54.2	
Aetiology					
Surgical	41	31.5	88	68.5	
129 cases (19.5%)					
Initial peak total bilirubin level	9.60	3.47	9.51	4.19	.7
Initial peak direct bilirubin level	6.52	2.49	6.47	2.39	.9
Initial ALT level	2.21	1.28	2.17	1.59	.4
Initial AST level	2.49	1.08	2.46	1.43	.07
Hepatocellular*	222	49.9	223	50.1	
445 cases (67.2%)					
Initial peak total bilirubin level	9.08	3.39	9.00	3.03	.9
Initial peak direct bilirubin level	6.47	2.24	6.27	2.23	.9
Initial ALT level	3.15	3.12	2.98	2.66	.3
Initial AST level	2.73	2.84	2.67	2.21	.09
Paucity of intrahepatic biliary radicals	39	44.3	49	55.7	
88 cases (13.3%)					
Initial peak total bilirubin level	11.74	3.89	11.13	3.95	.4
Initial peak direct bilirubin level	8.33	3.09	8.15	3.13	.8
Initial ALT level	2.46	1.09	109.28	53.17	.6
Initial AST level	2.41	1.05	2.37	1.12	.4

Initial peak total bilirubin level and direct levels represent the peak before receiving UDCA in first group and absolute peak in those who did not.

ALT = alanine aminotransferase measured in folds of upper normal, AST = aspartate aminotransferase measured in folds of upper normal, UDCA = ursodeoxycholic acid.

*Hepatocellular aetiology: Idiopathic neonatal hepatitis (NH) (n = 335, 50.6%), NH secondary to other disease (n = 110, 16.6%), hepatitis B virus infection (n = 21, 3.2%), hepatitis C virus (n = 5, 0.8%), cytomegalo virus infection (n = 28, 4.2%), syphilis (n = 1, 0.2%), toxoplasmosis (n = 4, 0.6%), herpes virus infection (n = 1, 0.2%), rubella (n = 1, 0.2%), sepsis associated cholestasis (n = 8, 1.2%), progressive familial intrahepatic cholestasis (PFIC) (n = 7, 1.1%), alpha one anti trypsin deficiency (n = 5, 0.8%), galactosemia (n = 7, 1.1%), tyrosinemia (n = 1, 0.2%), Neimann Pick syndrome (n = 7, 1.1%), glycogen storage disease (GSD) (n = 1, 0.2%), Zellweger syndrome (n = 1, 0.2%), fatty acid oxidation defect (n = 1, 0.2%), neonatal hemochromatosis (n = 1, 0.2%), metabolic hepatitis of undefined etiology (n = 10, 1.5%). Paucity of intrahepatic bile ducts (Alagille syndrome [n = 9, 1.4%], nonsyndromic [n = 40, 7.4%], and vanishing bile duct syndrome [n = 30, 4.5%]).

While withdrawal syndrome is only another serious complication of UDCA to be compiled to the other reported side effects as hepatitis, cholangitis, ascites, vanishing bile duct syndrome, liver cell failure, pruritus, severe watery diarrhea, immune-suppression, pneumonia, dysuria, death, mutagenic effects, genotoxicity, and

down-regulates cellular functions.^[5,7-9] UDCA unlicensed use in neonates and children is based on a lot of good intention, structurally flawed studies, wishful thinking despite absent evidence derived from well-structured randomized double blind case-control trials and being in the market for over 20 years. It is very peculiar that no authority attempted to study UDCA in children through well-structured randomized case-control trials, and the scientific merit of UDCA is derived from theoretical assumptions.^[12] It is also peculiar that the toxicity of UDCA in adults was only noted during the double blind case-control trial in 2009.^[5]

Table 2
Outcome of cholestasis among those who received UDCA and those who did not.

	Cases who did not receive UDCA N = 302		Cases on UDCA N = 360		P
	% 45.6	% 54.4	% 54.4	% 54.4	
Surgical cholestasis (n = 129)					
Successful	20	48.8	33	37.5	<.001
Improved	5	12.2	25	28.4	
Failed	16	39	18	20.5	
Death	0	0	12	13.6	
Neonatal hepatitis (n = 445)					
Successful	162	73	105	47.1	<.001
Improved	13	5.9	42	18.8	
Failed	34	15.3	66	29.6	
Death	13	4.5	10	5.9	
PIBD (n = 88)					
Successful	39	100	27	55.1	<.001
Improved	0	0	2	4.1	
Failed	0	0	17	34.7	
Death	0	0	3	6.1	

PIBD = paucity of intrahepatic bile ducts, UDCA = ursodeoxycholic acid.

4.3. Post-marketing studies (PMS) are a necessity

PMS are the prospective equivalent of our cohort study. PMS conveniently outline effectiveness and safety profile on real grounds of marketed indications, and provide information about effectiveness and safety in the other ethnic groups, countries, various age groups, and diseases.^[13,14] We recommend extension of PMS to include off-label use, and recommend regulation of off-label use by initiating the registry for Off-label Use Studies by National Drug Registration Bodies as a part of Post-marketing studies. We recommend obliging all off-label users to register the results, long and short-term effects upon subjects receiving these off-label medications, and how to reach those subjects, with informed consent of parent/caregiver. The registry would provide complete transparency and visibility to all to allow studying effectiveness and safety in every geographic area across its ethnic

Table 3
Complications of UDCA in neonates and infants with cholestasis.

	Cases who did not receive UDCA		Cases on UDCA		P	Risk	Confidence interval = 95%	
	N	%	N	%			Lower limit	Upper limit
	302	45.6	360	54.4				
Infectious								
Recurrent diarrhea	11	3.6	119	33.1	.000	12.298	5.568	27.162
Pharyngitis	1	0.3	29	8.10	.000	10.348	1.187	90.225
Pneumonia	3	1	27	7.5	.000	1.135	0.231	5.568
Bronchopneumonia	1	0.3	14	3.9	.001	2.837	0.262	30.766
Bronchitis	13	4.3	89	27.2	.000	5.919	3.001	11.675
Otitis media	4	1.3	23	6.4	.001	4.991	1.353	18.412
Dysuria	0	0	12	3.3	.025	10.37	1.342	80.289
Abscess	1	0.3	4	1.1	.26	0.106	0.008	1.372
Oral moniliasis	1	0.3	15	4.2	.001	3.853	0.411	36.084
Hepatic								
Liver cell failure and ascites	8	2.6	44	12.2	.000	5.753	2.370	11.050
VBD	4	1.3	14	3.9	.003	4.090	1.289	12.974
Intractable pruritus	2	0.7	8	2.2	.09	4.728	0.676	33.085
Gall stone formation	0	0	2	0.6	.29	1.36	0.000	-
Bleeding tendency	8	2.6	29	8.1	.002	5.560	1.281	24.127
Miscellaneous								
Fever	8	2.6	116	32.2	.001	11.915	4.277	33.191
Cyanosis	1	0.3	22	6.1	.000	7.178	0.884	58.301
Cough	20	6.6	152	42.2	.000	7.628	4.499	12.934
Vomiting	0	0	24	6.7	.003	21.5	2.891	159.88
Rash	1	0.3	9	2.2	.02	3.194	0.304	33.558
Hemolytic anaemia	0	0	10	2.8	.002	6.725	0.000	-

UDCA=ursodeoxycholic acid, VBD=vanishing bile duct.

groups. Experience is the least level of evidence.^[1,2] The off-label use is not a “right” for pediatricians.

4.4. Registries provide the evidence necessary to save children

Unregulated Off-label use is a calamity. The “grave” discovery of ineffectiveness and serious morbidity and mortality of UDCA in Egyptian children with cholestasis is not unique. Recently it was

“discovered” that off-label use of proton pump inhibitors (PPIs) and histamine2 receptor antagonists (H2-blockers), was not effective in otherwise healthy infants with gastro-esophageal reflux. “Gravely” it was found that children who received PPIs in the first 6 months of life had a 22% increased likelihood of fractures at a median 5.8 years following PPI use. When PPIs were used in combination with H2-blockers, the fracture risk escalated to 31%, and intake for 60 days to 150 days; and more than 150 days had a 23% and 42% greater hazard, respectively. We owe

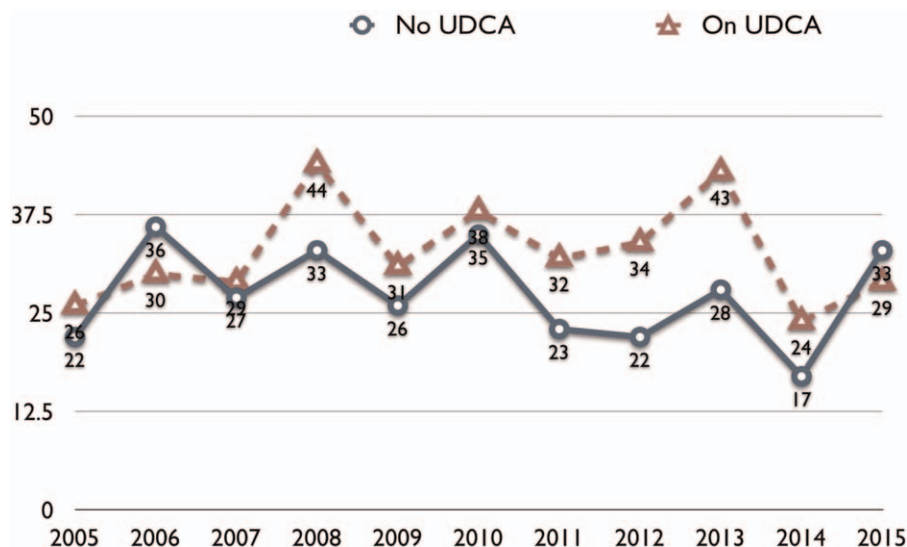


Figure 2. Annual rate of UDCA off-label use in infants with cholestasis of studied cohort through 2005 to 2015. UDCA=ursodeoxycholic acid.

the latter discovery of “children bone-deficiency tie to acid suppressors” to the “first-of-its-kind retrospective cohort study” of 874,447 children without diagnosed Gastroesophageal reflux disease born within the Military Health Care System from 2001 to 2013.^[3] Thus registries are indispensable for safer practice of medicine.

4.5. Old habits die hard despite change of UDCA package insert following initial publication of UDCA deleterious effects on Egyptian neonates

The habitual “off-label use” practice of UDCA in cholestasis in neonates and infants did not decline despite publishing 10 years ago, the evidence that UDCA was not effective in neonates and infants with cholestasis and was not safe, and the details of worse outcome of those who received UDCA, and the evidence that UDCA caused immune-suppression, severe watery diarrhea, dysuria, pneumonia, was hepatotoxic, caused pruritus, cholangitis, ascites, vanishing bile duct syndrome, liver cell failure, and death. We warned against sudden halt of UDCA as it causes a withdrawal syndrome upon sudden halt, and against the very tight dose margin between therapeutic dose and toxic dose.^[7-9]

4.6. Better safe than sorry

Studies demonstrating effectiveness of a specific drug in a specific age or disease cohort are not evidence to be “projected theoretically” on other disease or age entities; hence randomized case-controlled trials in children are a must. The cost of such trials are high, yet the morbidities and lost lives are the higher cost of off-label use. Sponsors should be allowed to raise funds for such trials. It is very grave to know that the UDCA-induced progression of disease and the deaths could have been prevented had UDCA been studied in children before its off-label and unlicensed use.

4.7. Off label experience on safety and effectiveness of medications is not recorded or archived, is wasted valuable information and is a major financial burden

It is surprisingly that most medications in children are used off-label, with lack of evidence of their safety or effectiveness. Unfortunately, 62% of medications used in outpatient prescription in children is off label along with 96% of cardiovascular-renal medications, 86% of pain medications, 80% of gastrointestinal medications, and 67% of pulmonary and dermatologic medications.^[15] Again 90% of prescribed medicines in neonates and 15% to 60% in infants are off label, and all the valuable information related to this use is lost and cannot be built upon.^[16]

All information related to the off label use in terms of safety, effectiveness, and interactions is not available, and not published or retrievable. Moreover, promotion of off label use of medications is illegal and settlements can mount to 1.4 billion dollars.^[17] Oncologists practice off-label prescription of anti-cancer medications and immunotherapy despite the lack of supportive data. Off-label prescribing held subjects from joining clinical trials that are ongoing as it provided another line of therapy, which results in a more refractory population, and more side effects and morbidity to patients. Off-label use of anticancer drugs in USA cost almost \$5 billion US dollars for the commonest 10 used cancer drugs.^[18,19]

4.8. Transitional period measures is recommended to replace need for extrapolation of pediatric use from adult drug trials by enforcement of post-marketing off-label use registries

As Food and Drug Administration (FDA) recognizes shortage of pediatric well-structured randomized case-control drug trials, FDA took the lead by allowing extrapolation from adult trials. FDA may approve drug pediatric effectiveness to be extrapolated from adequate and well-controlled studies in adults, but usually FDA recommends supply of other information obtained from pediatric patients.^[20]

Initiation of a transient period of registration of off-label use of medications in pediatric age would provide enough information to judicious increase of treatment options, discourage use of ineffective and unsafe medications, and allow for registration system maturation and creation of simpler system technologies for reporting, indexing, validation, specific associations with safety, effectiveness, drug interactions, effectiveness across ethnic diversity, fill gaps of knowledge and above all define venues for future research. The registries would reduce the personal weighing of benefits and risks for off-label use based on wild guessing, extrapolation from adult studies and/or professional experience, to be replaced by off-label medications use based on reason and robust evidence with well-calculated projected risk and benefits.

4.9. The retrospective nature of the study is a limitation

It was deemed extremely unethical by Ethical Committee standards to perform a prospective randomized case-control trial of UDCA in neonates with cholestasis to assure extent of harm inflicted on them. UDCA is a bile acid, that is at best adjuvant and is not a curative treatment, was not licensed for use in neonates and with previously known ineffectiveness; hence, a trial to assure UDCA extent of harm and morbidity is not heard of. Being retrospective, did not allow assessment of lithocholic acid in the group that received UDCA. Lithocholic acid is the break-down bile acid of UDCA. Lithocholic acid can be toxic to hepatocytes and lead to segmental bile duct injury up to causing liver cell failure in those with compromised sulfation and death.^[21]

4.10. How to apply this knowledge in routine clinical practice?

Until measures to enforce off-label use registries on national level are enforced, hospitals should be encouraged to set their own off-label drug use registries. Drug induced diseases and complications are not always reversible, this irreversibility is not against the diagnosis of drug induced damage.^[22] UDCA induced liver damage in neonates and infants with cholestasis was not reversible, UDCA should not be used in pediatric age group.

5. Conclusions

UDCA is not effective in neonates and infants with cholestasis, and its use compromises chance of cure, and is associated with serious morbidity and mortality. UDCA should be contraindicated in neonates and infants with cholestasis. Post-marketing studies are mandatory. Off-label use of medications in children should be replaced by evidence-based Off-label Use Registry Studies with informed consent of parents under control of national regulatory bodies. It is very grave and sad that the off-label UDCA-induced progression of disease, morbidity and mortality in our studied cohort were absolutely preventable.

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Author contributions

Conceptualization: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti, Ahmed M. Badr, Hend El Hosainy Abd El Baky.

Data curation: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti, Sally Talaat Mostafa El Sorogy, Hend El Hosainy Abd El Baky.

Formal analysis: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti, Sally Talaat Mostafa El Sorogy, Ahmed M. Badr.

Investigation: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti, Ahmed M. Badr, Sally Talaat Mostafa El Sorogy, Hend El Hosainy Abd El Baky.

Methodology: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti, Ahmed M. Badr, Hend El Hosainy Abd El Baky.

Project administration: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti.

Resources: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti, Ahmed M. Badr, Hend El Hosainy Abd El Baky.

Supervision: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti, Ahmed M. Badr, Hend El Hosainy Abd El Baky.

Visualization: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti, Ahmed M. Badr, Sally Talaat Mostafa El Sorogy, Hend El Hosainy Abd El Baky.

Writing – original draft: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti, Sally Talaat Mostafa El Sorogy, Ahmed M. Badr, Hend El Hosainy Abd El Baky.

Writing – review & editing: Magd Ahmed Kotb, Dalia Mosallam, Iman Hassan Draz, Christine William Shaker Basanti, Sally Talaat Mostafa El Sorogy, Ahmed M. Badr, Hend El Hosainy Abd El Baky.

Dalia Mosallam orcid: 0000-0002-4026-4217.

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