Supplementary Table 1. Summarizing table of all articles discussing altered drug absorption in adults.

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
ANTICONVULSANTS											
Bauer[1], 1982	Prospective observational	Phenytoin A: 1000 mg loading dose followed by 300 mg B: 400 mg	Neurosurgery patients Groups A1: phenytoin treatment for 14 days. TF was discontinued on day 8 A2: phenytoin treatment for 14 days. TF was started on day 8 B: healthy subjects	25 A1: 10 A2: 10 B: 5	A.1: 80 A.2: 70 B: 100	A.1: 25.3 ± 4.7 A.2: 27.6 ± 5.3 B: 23.2 ± 3.1	NR	NR	Initial (µg/ml): A.1, day 8: 2.59 ± 0.96 A.1, day 14: 10.22 ± 2.90 A.2, day 8: 9.80 ± 3.27 A.2, day 14: 2.72 ± 1.09 B, TF: 0.70 ± 0.26 (after 24 h) B, no TF: 3.40 ± 0.45 (after 24 h)	• Interactions with the TF formula (Isocal®)	• Decreased concentrations in all groups when co-administered with TF* • Concentrations (random) increased when TF was held for two h before and after drug administration
Sneed et al.[2], 1988	Retrospective observational	Phenytoin	Brain-injured patients Investigations with TF	11	NR	NR	NR	NR	Exact numbers NR	• Interactions with the TF formula	• Seven patients had altered serum phenytoin levels due to TF. All needed higher doses to maintain desirable drug concentrations. Six of these showed a rise when TF was held* • TDM is important in this population
Faraji et al.[3], 1998	Retrospective observational	Phenytoin	Brain-injured patients Groups A: TF was held for 1 h after drug administration B: continuous TF	22 A: 13 B: 9	91	36 (16-65)	NR	NR	Mean (µg/ml): A: 14.4 ± 4.7 B: 9.2 ± 6.8	• Interactions with the TF formula	• Higher concentrations in group A* • No difference in means for dose mg/24h or dose mg/kg between the groups* • Similar results after adjusting for serum albumin level • No difference in mean intake of TF

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
											formula*
Sohrevardi et al.[4], 2008	Prospective interventional	Phenytoin Steady-state dose, 300 mg QD	Patients with acute brain injury Groups A: continuous TF B: TF was held for 2 h before drug administration	30 A: 15 B: 15	A: 60 B: 73	A: 36.2 ± 15 B: 35.8 ± 13.9	NR	NR	Steady state (µg/ml): A: 6.3 ± 4 B: 24.7 ± 9.4	• Interactions with the TF formula	• Subtherapeutic levels in 70% of the patients in group A* • Supratherapeutic levels in 70% of the patients in group B* • TDM is important in this population
Taylor et al.[5], 1993 (letter)	Case report	Phenytoin Day 3-14: 368 mg/d phenytoin base Day 15-39: 360 mg/d suspension Day 40-75: 368 mg/d phenytoin base	A 60 kg, mechanically ventilated patient who suffered from a generalized seizure followed by status epilepticus Drug administration: Day 3-14: IV Day 15-39: PO, suspension Day 40-75: PO, tablets Day 10-20: NG feeding Day 20-33: Fresubin liquid food concentrates Day 34 on: normal eating	1	100	67	NR	NR	Corrected levels (µg/ml): IV: 11-19 PO, susp: 5-11 PO, tablet: 14-16 Lowest Concentration: Day 30	• Interactions with the TF formula (Fresubin®)	• Reduced concentrations when the suspension was co-administered with TF • Concentrations recovered after change to solid food intake and tablets
Boulamery et al.[6], 2010 (abstract)	Case report	Phenytoin 300 mg QD was gradually increased to 600 mg QD	Critical ill patient at the ICU for diet-induced encephalopathy with seizures Enterally fed via a jejunal tube, drugs administered through the tube	1	0	40	NR	NR	Undetectable or subtherapeutic	• Less phenytoin absorption in jejunum than duodenum • Interactions with the TF formula • The GI transit may have been affected by enteral feedings • Interactions with other drugs • Lowered pH in GI which decreased the absorption	• Subtherapeutic concentrations and therapy failure • TDM is necessary in this population

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Maynard et al[7], 1987	Case report	Phenytoin, suspension A: 1.0-1.2 g/day B: 1.0-1.2 g/day C: 1.6-1.8 g/day D: 600 mg/day E: 300-400 mg/day	Patients who suffered from a large cerebral hemorrhage Five investigations were made A: Osmolite®, continuous TF B: Osmolite®, TF held two hours before and after drug administration C: Isocal®, TF held 09:00-17:00, drug given at 09:00 and 17:00 D: Meat-based formula, TF held 09:00-17:00, drug timing as with Isocal® E: Meat-based formula, continuous TF, drug at 09:00 Weight NR	1	0	47	NR	NR	C_{max} (µg/ml): A: 9 B: 9 C: 14 D: 19 E: 9	• Interactions with feeding formula	• Higher doses were needed to achieve therapeutic concentrations when co-administered with Isocal® • Therapeutic concentrations were obtained with higher doses of phenytoin with Isocal® or Osmolite® • Therapeutic levels achieved with lower doses when given with meat-based formula
Rodman et al.[8], 1995	Case report	Phenytoin Day 11: 500 mg loading dose, followed by 100 mg q6h Day 12: additional 500 mg loading dose Day 15-20: 200 mg q12h Day 21-33: 125 mg TID	Patient with generalized tonic-clonic seizure disorder Investigations Day 11: IV Day 12: IV Day 15: IV Day 21-33: jejunostomy tube Continuous TF (Jevityv®) Weight: 64 kg	1	0	29	NR	NR	Random (µg/ml): Day 11: 5.6 Day 12: NR Day 15: 19.1 Day 21: 9.3 Day 33: <2.5	• Drug interactions • Possible interactions with tubing • Interactions with TF formula • Distal jejunostomy tube placement	• Subtherapeutic concentrations when phenytoin was given with enteral nutrition compared to IV administration

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Mink et al.[9], 2011	Prospective observational	Valproic acid or Levetiracetam 3 g QD, IV then liquid, both drugs	Patients at the ICU who suffered with, or were in high risk of developing, seizures Groups A: valproic acid B: levetiracetam Investigations were made for both IV and TF administration	35 A: 17 B: 18	40	51 ± 11.7	A: NR B: 70.3	NR	Mean (µmol/L): A: IV: 433 ± 92 TF: 454 ± 131 B: IV: 160 ± 51 TF: 113 ± 58	• Possibly GI dysfunction	• TF administration of levetiracetam results in lower concentrations* • Valproic acid absorption was not affected • Lower concentrations in group A when co-administered with meropenem*
ANTIMICROBIALS											
Yuk et al.[10], 1990	Prospective observational	Ciprofloxacin 750 mg BID	Critical ill patients at the ICU Groups A: ND B: NG C: G Continuous TF, interrupted only for dose administration	7 A: 4 B: 2 C: 1	A: 100 B: 100 C: 100	A: range 71-76 B: 61, 74 C: 47	NR	Mean AUC (mg*h/L): A: 25.35 ± 8.28 B and C: 11.27 ± 5.39	C_{max} (mg/L): A: 4.60 ± 1.11 B and C: 2.57 ± 1.00	• Possible degradation of ciprofloxacin in the stomach and reduced absorption due to unfavorable conditions	• Greater absorption in group A compared with group B and C • With both NG and G administration resulting in lower Cmax and AUC values it may be reasonable to consider a dose greater than that studied.
Cohn et al.[11], 1995	Prospective observational	Ciprofloxacin 750 mg BID	Abdominal postoperative patients at the SICU Drug administration via NG. Enteral feeding was held for 1 h after drug administration	8 (9 enrolled, records lost for one patient)	12.5	Mean: 74 Range: 48-92	NR	Mean AUC (mg*h/L): Dose one: 3.48 ± 3.15 Dose four: 17.74 ± 15.17	C_{max} (mg/L): Dose one: 0.55 ± 0.59 Dose four: 2.14 ± 1.50	• Non-intact GI tract directly after surgery • Delayed gastric emptying • Impaired GI perfusion	• Poor absorption during the first 12 h • AUC and C_{max} were higher after dose four* • C_{max} lower than healthy subjects from other studies
Cohn et al.[12], 1996	Prospective observational	Ciprofloxacin 750 mg BID	Mechanically ventilated patients at the ICU with documented pneumonia Drug administration via NG	7	71	Mean: 52.1 Range: 34-71	NR	Mean AUC (mg*h/L): Dose one: 9.90 ± 2.05 Dose four:	C_{max} (mg/L): Dose one: 2.29 ± 0.24 Dose four: 2.23 ± 0.39	• Interactions with the TF formula (Pulmocare®) • Inter-patient variability	• Moderate and variable absorption in ICU patients • Serum concentrations were above MIC for many pathogenic bacteria • C_{max} and AUC comparable to those seen in healthy subjects after 500 mg, single dose in another study

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
			TF in all patients					10.63 ± 2.11			
De Marie et al.[13], 1998	Prospective observational	Ciprofloxacin TF: 750 mg BID IV: 400 mg BID	Critically ill patients with severe GNIAI managed at the ICU Investigations were made for both IV and TF (NG or ND) administration Continuous TF	5	NR	Range: 27-76	53.1 (43.5-62.8)	Mean AUC (mg*h/L): TF: 19.1 (10.8-27.5) IV: 19.3 (11.8-26.7)	$C_{max, ss}$ (mg/L): TF: 3.2 (1.8-4.6) IV: 6.8 (3.9-9.8)	• Interactions with the TF formula	• The AUC provided by enteral administration was like that provided by IV administration • Authors concluded that adequate bioavailability and AUC was observed with 750 mg BID enteral dose
Mimoz et al.[14], 1998	Prospective observational	Ciprofloxacin TF: 750 mg BID IV: 400 mg BID	Mechanically ventilated patients at the SICU Investigations were made for both IV and NG administration Continuous TF	12	92	41 (19-75)	44 (31-82)	Mean AUC (mg*h/L): NG: 8.4 (3.6-53.4) IV: 10.3 (3.3-34.6)	C_{max} (mg/L): NG: 2.3 (0.7-5.8) IV: 4.1 (1.5-7.4)	• Variability between patients • Interactions with the TF formula	• C_{max} was reduced with NG administration but AUC was similar between routes. • The IV dose resulted in C_{max}/MIC values consistently in or above the 10-12 range, but the NG was less consistent • A switch from IV to NG administration may need to be restricted to patients where assessments of drug levels are available
Debon et al.[15], 2002	Prospective interventional	Ciprofloxacin immediate-release suspension, 500 or 750 mg BID	Mechanical ventilated patients at the ICU with documented pneumonia Groups A: 500 mg BID B: 750 mg BID NG administration Continuous TF	20 A: 10 B 10	A: 30 B: 40	A: 63 (50-90) B: 65 (48-88)	NR	Mean AUC (mg*h/L): A: 24.7 (12.9-36.2) B: 28.9 (18.3-47.5)	C_{max} (mg/L): A: 2.6 (1.2-4.3) B: 3.5 (1.5-5.9)	• Absorption was not altered by TF formula	• Both dosages resulted in C_{max}/MIC values above the minimum needed for treating susceptible pathogens including: *H. influenzae*, *E. coli*, *P.mirabilis*, *Enterobacter spp.* and *K. pneumoniae* • The oral suspension appeared to have greater bioavailability than crushed oral tablets (750 mg), compared with results from other trials

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
De Smet et al.[16], 2012	Prospective observational	Moxifloxacin 400 mg QD (One patient received 600 mg due to morbid obesity)	Critically ill patients at the ICU with documented pneumonia Investigations were made for both IV and TF administration	4	50	41-64	NR	AUC_{0-24} (mg*h/L): TF: 40.13 (16.80-51.51) IV: 51.21 (23.46-72.90)	C_{max} (mg/L): TF: 4.07 (2.86-5.95) IV: 7.27 (4.47-11.34)	• High inter-individual variability	• Enteral administration is not bioequivalent to IV administration • Low AUC/MIC values seen may suggest that efficacy is not achieved with enteral administration • Both AUC/MIC and C_{max}/MIC values attained with enteral administration did not meet the minimum values required for treating common pathogens
Kees et al.[17], 2013	Prospective observational	Moxifloxacin 400 mg QD	A population PK-model was conducted on patients at the ICU and SICU Initial treatment with IV, followed by NG administration Continuous TF	25 IV: 25 NG: 16	IV: 80 NG: 87.5	IV: 64 (18-78) NG: 60.5 (18-78)	76.4	NR	NR	• Crushed tablet administered through NG tube	• Enteral bioavailability was lower, and more variable compared to healthy volunteers • Authors concluded enteral administration may not be reliable with ICU patients
Beyssac et al.[18], 1991	Prospective observational	Cefroxadine, single dose A and B: 1000 mg C: 250 mg	Trauma patients Groups A: TF formula 1 B: TF formula 2 C: healthy subjects, data from a previous study NG Administration Continuous TF Crossover design	A and B: 18 C: 6	A and B: 78	A and B: 17-40 C: 22-50	NR	$AUC_{0-\infty}$ (µg*h/ml): A: 37.5 ± 10.50 B: 42.18 ± 13.50 C: 48.9 ± 5.95	C_{max} (mg/mL): A: 18.13 ± 7.02 B: 20.08 ± 8.51 C: 25.05 ± 9.92	• Impaired splanchnic flow • Weaker migrating motor complex due to TF • Reduced intralumenal diffusion and absorption due to low temperature on the TF formula	• AUC and C_{max} were normalized to a dose of 1000 mg in group C • Lower AUC in group A compared with C* • C_{max} did not show differences between groups A and B compared to group C
ANTIFUNGALS											
Rosemurgy et al.[19], 1995	Prospective interventional	Fluconazole 100 mg, single dose, both routes	Trauma and postoperative patients at the SICU Groups A: NG or NJ B: IV	18 A: 8 B: 10	A: 100 B: 80	A: 53 ± 17.7 B: 43 ± 12.4	77	Mean AUC (mg*h/L): A: 35 ± 16.0 B: 46 ± 19.7	C_{max} (mg/L): A: 1.55 ± 0.469 B: 1.48 ± 0.364	• DI dysfunction	• AUC was non-significantly lower after enteral administration than IV • Slightly higher C_{max} was observed with enteral administration over IV • Bioavailability is reduced compared to healthy individuals, though still substantial

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
											• Trend to lower systemic availability with enteral administration may be overcome with increased doses
Zhou et al.[20], 2001	Prospective observational	Fluconazole 200 mg, single dose, both routes	Critically ill patients at the ICU Investigations were made for both IV and TF (NG or ND) administration Continuous or bolus TF	5	60	60.4 Range 46-80	77 ± 44	Mean AUC (mg*h/L): TF: 202.6 (115.03-385.65) IV: 321.1 (102.93-471.36)	C_{max} (mg/L): TF: 4.3 (2.81-5.53) IV: 4.7 (1.33-10.13)	• Inter-individual variability	• Lower AUC and C_{max} after TF administration • Authors have concluded that fluconazole given through TF should give adequate serum concentrations for the treatment of fungal infections
Barquist et al.[21], 2007	Prospective observational	Fluconazole 400 mg loading dose followed by 200 mg QD	Postoperative abdominal trauma patients at the TICU Groups A: postoperative laparostomy patients B: postoperative patients with closed abdomen Investigations were made for both IV and TF administration	16 A: 6 B: 10	A: 83 B: 90	A: 38 ± 9 B: 48 ± 18	A: 51.3 ± 29.7 B: 63 ± 19.5	Mean AUC (mcg/ml): A, TF: 53.7 ± 18.5 A, IV: 115.1 ± 34 B, TF: 106.2 ± 59.6 B, IV: 166.9 ± 71.5	C_{max} (mcg/ml): A, TF: 4.2 ± 1.5 B, TF: 7.0 ± 3.8	• Impaired absorption capacity due to open abdomen • Hyper-metabolic state (common in this patient population)	• Lower enteral AUC in group A after TF administration* • Lower C_{max} in group A* • Lower bioavailability in group A • Variated and unpredictable bioavailability in the study population • IV administration may give more reliable serum levels in the first 2 weeks after trauma-related laparostomy
Störzinger et al.[22], 2012	Prospective observational	Posaconazole 200 mg q6h	A population PK-model on abdominal surgery patients at the SICU Drug administration via NG. Continuous TF PPI were given to all	15	40	58 (41-79)	NR	NR	C_{max} (µg/L): 295 ± 152 Mean (µg/L): 175 ± 77	• Simultaneously treatment with PPI in all patients • GI dysfunction • Malabsorption • Interactions with feeding tube	• Target concentration was 700 µg/L, and no patient displayed this value by day 7. • Inadequate and unpredictable serum concentrations were observed • The authors concluded that the use of enteral posaconazole is likely not appropriate in critically ill surgical

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
			patients for stress ulcer prophylaxis								patients
Ray et al.[23], 2011	Prospective interventional	Posaconazole 200 mg QID or 400 mg BID	Critically ill patients at the ICU Groups A: 200 mg QID B: 400 mg BID Drug administration via NG. Continuous TF PPI were given to all patients for stress ulcer prophylaxis	27 A: 14 B: 13	A: 79 B: 62	A: 44.8 ± 22.7 B: 56.8 ± 17.3	NR	After first dose (µg*h/L): A: 299 ± 198 B: 761 ± 242	C_{max} (µg/L): A: 84 ± 50 B: 111 ± 45	• Highest plasma posaconazole concentrations seen in patients with frequent TF interruptions • Co-administration with PPI • Lower AUC when co-administration with phenytoin	• Impaired absorption. Desirable concentration for prophylaxis is 250 µg/L. The majority failed to achieve this target concentration • C_{max} in healthy subjects, 200 mg: ~ 325 µg/L (from different study data) • Systemic exposure was lower than seen in healthy subjects *(also from other study data)* • TDM recommended
Kintzel et al.[24], 1995	Case report	Itraconazole 400 mg QD, intralipid suspension Followed by 600 mg QD, citric acid suspension	A: mechanically ventilated patient at the ICU who had undergone allogeneic BMT Drug administration via gastric tube	1	100	38	NR	NR	(µg/L): Predose, 400 mg: NR Postdose, 400 mg: 5 Predose 600 mg: 72 Postdose, 600 mg: 97	• Impaired solubility due to increased gastric pH • Delayed gastric emptying • Impaired GI function and perfusion	• Neither suspension gave desirable serum concentrations • Citric acid suspension may have resulted in greater absorption compared to the intralipid suspension in case A
		Itraconazole 600 mg QD, intralipid suspension on readmission	B: mechanically ventilated patient at the ICU who had undergone allogeneic BMT Drug administration via gastric tube	1	100	29			(µg/L): Baseline: 29 Predose: 19 Postdose: 18		

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Olsen et al.[25], 2008	Prospective interventional	Lansoprazole, 30 mg	Mechanically ventilated patients at the ICU Groups A: IV B: NG Enteral feeding was held 1 h after drug administration	19 A: 9 B: 10	A: 56 B: 60	A: 59.7 ± 11.7 B: 56.8 ± 16.2	76	AUC_{0-24} (ng*h/ml) A, day 1: 2102 ± 380 A, day 3: 2198 ± 321 B, day 1: 1597 ± 369 B, day 3: 1992 ± 474	C_{max} (ng/ml) A, day 1: 1127 ± 234 A, day 3: 1244 ± 207 B, day 1: 993± 230 B, day 3: 1103 ± 299	• GI dysfunction	• Lower AUC in group B on both day 1 and 3* • Lower C_{max} in group B on both day 1 and 3* • TF administration had a faster onset and maintained gastric pH >4 longer than IV administration at both 24 and 72 h* • Enteral lansoprazole suppressed acid to a greater extent than IV
Tanswell et al.[26], 1990	Prospective observational	Pirenzepine IV: 10 mg PO: 50 mg	Groups A: critically ill patients at the ICU B: healthy subjects Investigations were made for both IV and PO administration in both groups	39 A: 27 B: 12	A: 74 B: 100	A: 60 ± 17 B: 36 (25-46)	A: 28 ± 13 B: 14 ± 3.5	NR	NR	• GI dysmotility may prolong the residence time of pirenzepine in the GI tract	• Higher bioavailability in critically ill patients compared with healthy subjects*
CARDIOVASCULAR MEDICATIONS											
Woodcock et al.[27], 1981	Prospective observational	Verapamil PO: 80 mg IV: 5 mg	Groups A: patients with liver disease B: patients at the ICU C: healthy subjects Investigations were made for both IV and PO administration	8 A: 4 B: 2 C: 2	NR	16-64	A: 3.8-63.8 B: 13.2-13.6 C: 17.5-21.0	AUC (ng*min/ml): A, IV: 5,952-13,860 A, PO: 8,467-60,741	NR	• Not discussed	• Data for bioavailability and AUC were only obtained from 4 patients in group A and 2 each in groups B and C • Large differences in PK - clearance was reduced in group A, and increased in group B • Clinically significant alterations in verapamil elimination was observed in groups A and B

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
								B, IV: 1,179-1,983 B, PO: 2,484-4,324 C, IV: 3,979-7,142 C, PO: 11,040-11,970			
Schoergenhofer et al.[28], 2017	Prospective interventional	ASA A: 81 mg BID B: 100 mg BID C: 100 mg BID	Critically ill patients at the ICU, diagnosed with HTPR Groups A: PO, chewable tablet B: IV C: PO, enteric-coated tablet Treatment for one day	30 A: 10 B: 10 C: 10	51	67 ± 13	NR	NR	C_{1h} ASA (ng/ml) A: 202 (0–720) B: 220 (110-607) C: 143 (0-255)	• Reduced GI motility	• Higher concentration in group B compared with C • Similar concentrations in group A and C • Platelet aggregation did not differ between the groups • Oral formulations resulted in highly variable absorption
Součková et al.[29], 2013	Prospective observational	Clopidogrel 600 mg, loading dose	Patients who suffered from CAD Groups A: PO, intact tablet. Had undergone planned PCI with stent implantation B: NG. Critically ill after CPR and acute PCI with stent implantation	19 A: 10 B: 9	A: 60 B: 67	A: 72 (55–86) B: 66 (47–81)	Exact numbers NR Impaired in group B*	NR	[$CLP_{metabolite}$] (ng/mL) *A: 18,455 (18,146-22,198)* *B: 11,906 (0-17,397)*	• GI dysfunction • Delayed gastric emptying • Decreased splanchnic perfusion	• Impaired bioavailability in group B* • Group B: four patients had undetectable concentrations; remaining patients had delayed absorption • All patients reached clinical inhibition in group A; two patients reached it in group B* • Platelet inhibition after 24h: group A 70%, group B 26%. Clinically effective level: >50%. • Increased risk of stent thrombosis in critically ill patients
OTHER MEDICATIONS											

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Bourne et al.[30], 2008	Prospective interventional	Melatonin 10 mg, oral liquid	Mechanically ventilated patients at the ICU Groups A: placebo B: melatonin TF administration	21 A: 9 B: 12	 A: 58.3 B: 33.3	 A: 58.7 ± 12.5 B: 69.9 ± 12.0	NR	AUC_{0-24} (ng*h/L): B: 29,979	C_{max} (ng/L): B: 14,974	• Melatonin appeared to be rapidly absorbed	• A higher C_{max} was observed compared with healthy subjects from other studies • Supratherapeutic morning concentrations seen and authors expressed concern regarding possible carryover effects
Bellapart et al.[31], 2016	Prospective interventional	Melatonin 3 mg loading dose followed by 0.5 mg q1h (total 6 mg)	Critically ill patients Groups A: melatonin B: placebo NG administration	13 A: 7 B: 6	NR	55 (35-78)	NR	NR	Group A: generally supra-physiological concentrations Group B: frequently undetectable	• High dose	• Exogenous administration resulted in supra-physiological concentrations in critically ill patients • Good oral bioavailability in critically ill patients
Mistraletti et al.[32], 2010	Prospective interventional	Melatonin 3 mg	Mechanical ventilated patients at the ICU NG or NJ administration	12 A: 6 B: 6	A: 83 B: 83	A: 62 (58-71) B: 74 (56-81)	NR	AUC (pg*h/ml): 28,231	C_{max} (ng/L): 11,039	• Crushed tablet • NG administration • Continuous TF • Prokinetic drugs and post-pyloric access in 3 patients	• Melatonin levels were impaired before treatment started • Concentration peak reached a higher level and was reached faster in critically ill patients than healthy subjects • No excessive sleepiness reported
Mistraletti et al.[33], 2019	Prospective interventional	Melatonin 3 mg, all groups	Mechanical ventilated patients at the ICU Groups A: NG/NJ, crushed and suspended tablet B: NG/NJ, lyophilized powder suspension C: transdermal	21 A: 7 B: 7 C: 7	A: 86 B: 71 C: 71	A: 69 ± 13 B: 71 ± 12 C: 73 ± 5	NR	AUC (ng*h/L): A: 44,441 B: 157,386 C: 3,142	C_{max} (ng/L): A: 26,813 B: 61,234 C: 388	• Lyophilized suspension lymphatically absorbed	• Avoidance of hepatic first metabolism with suspension • Higher AUC in group B compared with group A and C* • Higher C_{max} in group B and compared with group A and C* • Enteral administration adequate to obtain pharmacological levels

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Polito et al.[34], 2016	Prospective, observational	Fludrocortisone 50 µg, single dose	A population PK-model on patients with septic shock at the ICU Groups are presented depending on concentrations A: detectable B: undetectable Drug administration via NG	21 A: 14 B: 7	A: 56 B: 29	A: 65 (57-75) B: 55 (54-65)	NR	$AUC_{0-\infty}$ (µg*h/L): A: 1.25 (95% confidence interval 1.09-1.46)	C_{max} (µg/L): A: 0.19 ± 0.11	• Simultaneous treatment with PPI (drug ionization dependent on gastric pH)	• Serum concentrations were undetectable in one-third of the patients • High inter-individual variability

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Berger et al.[35], 2000	Prospective observational	Acetaminophen 1000 mg	Postoperative cardiac surgery patients Groups A: normal hemodynamic status. Managed at the high-dependency unit. B: hemodynamically unstable. Mechanically ventilated, managed at the ICU C: healthy subjects Drug administration via NG or PP	45 A: NG, 11; PP, 5 B: NG, 17; PP, 6 C: 6	NR	A: 57 ± 10 B: 69 ± 8 C: 37 ± 6	NR	AUC_{240} (unit not listed): A, NG, day 1: 892 ± 926 A, NG, day 3: 2262 ± 502 A, PP, day 1: 2350 ± 983 A, PP, day 3: NR B, NG, day 1: 826 ± 384 B, NG, day 3: 1781 ± 853 B, PP, day 1: 2513 ± 870 B, PP, day 3: 2375 ± 590 C, day 1: 2075 ± 509 C, day 3: NR	C_{max} (mg/ml): A, NG, day 1: 3.9 ± 2.3 A, NG, day 3: 18.6 ± 4.6 A, PP, day 1: 26.9 ± 10.3 A, PP, day 3: NR B, NG, day 1: 5.0 ± 2.8 B, NG, day 3: 12.5 ± 7.8 B, PP, day 1: 22.8 ± 9.0 B, PP, day 3: 26.9 ± 8.1 C, day 1: 16.5 ± 3.7 C, day 3: NR	• Delayed gastric emptying/pyloric closure • Authors concluded that hemodynamic instability does not preclude intestinal absorption • Opiates, especially on day 1 (morphine doses low after day 1)	• Large interpatient variability observed • AUC and C_{max} were impaired in group A and B on day 1 after NG • AUC and C_{max} in group A and B were similar to C on day 1 after PP • AUC in group A and B were similar to healthy subjects on day 3 • The increase in AUC between day 1 and 3 was significant in group A and B after NG*
Ariano et	Prospective	Acetaminophen	Critically ill patients	12	75	60 ± 15	75% (53-	NR	NR	NR	• The relative bioavailability of

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
al.[36], 2009 (abstract)	observational	suspension, 650 or 975 mg	NG administration				85%)				acetaminophen in critically ill patients was 75%
Mojtahedzadeh et al.[37], 2008	Prospective interventional	50 IU of insulin Metformin 1000 mg BID	Critical ill patients with SIRS and hyperglycemia Groups A: insulin IV B: metformin PO C: insulin + metformin	33 11 in each arm. Deaths occurred in each group leaving: A: 7 B: 9 C: 8	NR	A: 41.5 ± 19.5 B: 47.5 ± 14 C: 48.5 ± 14.5	NR	AUC (ng*h/ml): B: 6,710 ± 1,056	C_{max} (ng/ml): B: 970 ± 185	• GI dysfunction • Hypoperfusion • Hypomotility during hospitalization	• Deficit in oral metformin absorption in critically ill patients observed • AUC and C_{max} were lower than healthy subjects or outpatient subjects • No significant difference in the glycemic control was observed between the groups

ASA, acetylsalicylic acid; AUC, area under curve; BID, “bis in die”, twice a day; BMT, bone marrow transplant; C; concentration; CAD; coronary artery disease; CPR, cardiopulmonary resuscitation; DHA, docosahexaenoic acid; EPA, eicospentaenoic acid; F; bioavailability; G, gastrostomy tube; GI, gastrointestinal; GNIAI, gram-negative intra-abdominal infections; HTPR; high on-treatment platelet reactivity; ICU, Intensive Care Unit; IU, international unit; IV, intravenous; MIC, minimum inhibitory concentration; N, number of participants in the study; ND, nasoduodenal tube; NG, nasogastric tube; NJ, nasojejunal tube; NR, not reported; PCI; percutaneous coronary intervention; PK, pharmacokinetics; PO; per oral; PP, postpyloric tube; PPI, proton pump inhibitors; "q_h", "q" stands for "quaque" and "h" indicates the number of hours between every dosing; QD, “quaque die, one a day; QID, “quater in die”, four times daily; SICU, Surgical Intensive Care Unit; SIRS, systemic inflammatory response syndrome; TDM, therapeutic drug monitoring; TF; tube feeding; TICU, Trauma Intensive Care Unit; TID, “ter in die”, three times a day. * Statistically significant

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Bioavailability of Orally Administered Drugs in Critically Ill Patients

Supplementary Table 2: Summarizing table of all articles discussing unaltered drug absorption.

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Antimicrobials											

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Rebuck et al.[1], 2002	Prospective observational	Levofloxacin 500 mg Q24H 2 patients received 250 mg Q24H	Critically ill patients (ICU) Groups A: IV levofloxacin, all patients B: Oral levofloxacin, subset of patients	Total: 26 A: 26 B: 10	83	51 ± 12	95 ± 8	AUC (mg*hr/L) A: 66.1 ± 15.7 A, 10 patients that later received PO: 62.4 ± 6.3 B: 60.3 ± 16.3	C_{max} (mg/L) IV: 7.5 ± 0.8 PO: 5.5 ± 1.1	• No significant GI dysfunction in study population	• Increases in C_{max} and AUC were found in critically ill patients given IV levofloxacin compared to data from healthy volunteers (historical)* • Oral administration appears to result in AUC to IV administration, however C_{max} was reduced with oral administration* • Authors concluded that C_{max}/MIC and AUC/MIC ratios would be appropriate for susceptible *S. pneumoniae* and gram-negative pathogens including *E. coli, K. pneumoniae, H. influenza*, and *Enterobacter sp.* using IV administration in ICU patients. No conclusion was made using oral administration
Kanji et al.[2], 2003	Prospective Interventional	Gatifloxacin 400 mg Doses given either IV or NG, then given the opposite route after 72-hr washout	Critically ill patients NG Feeds A: Continuous TF B: Interrupted TF	16 A: 8 B: 7 4 in each group got IV first and 4 got NG first 1 patient in B excluded with low serum drug levels after IV dose	56 (sex of 1 patient NR)	49 (18-67)	A: 109.0 (86.2-142.1) B: 98.5 (61.1-119.7)	AUC (µg*h/mL) A, IV: 39.7 (22.5-63.1) A, NG: 34.2 (23.9-85.5) B, IV: 39.5 (24.1-63.1) B, NG: 38.0 (20.1-48.5)	C_{max} (µg/mL) A, IV: 4.45 (3.05-5.39) A, NG: 3.31 (2.18-6.60) B, IV: 4.65 (3.03-7.78) B, NG: 2.62 (1.15-6.60)	• Delayed gastric emptying or compromised mesenteric perfusion • Loss of medication during preparation and administration • Physiologic alterations over the 72-hr washout period	• No significant differences in the average bioavailability between the continuous TF group and the interrupted TF group. However, a wide range was seen, and some patients had F <70% • Continuous enteral nutrition did not appear to reduce gatifloxacin bioavailability • Bioavailability of enteral gatifloxacin in critically ill patients appears highly variable, and empirical treatment may not be appropriate for all ICU patients.

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Chin et al.[3], 1995	Prospective Observational	Trimethoprim 15 mg/kg Sulfamethoxazole: 75 mg/kg Drugs given IV or PO, then switched to receive the equivalent dose by the alternate route	Critically ill and non-critically ill AIDS patients with *P. carinii* pneumonia A: Critically ill, requiring mechanical ventilation B: Non-critically ill Enteral doses given PO unless patient unable to take PO tablets Patients on TF had feeds held while the drugs were administered	A: 8 B: 9	A: 100 B: 100	A: 37 ± 8 B: 37 ± 9	A, trimethoprim: 97.5 ± 22.4 A, sulfamethoxazole: 86.2 ± 17.9 B, trimethoprim: 101.8 ± 22.7 B: sulfamethoxazole: 99.1 ± 20.5	NR	C_{max} (µg/mL) A, IV trimethoprim: 8.1 ± 2.6 A, IV sulfamethoxazole: 163.6 ± 21.5 A, PO trimethoprim: 6.6 ± 1.5 A, PO sulfamethoxazole: 145.8 ± 42.0 B, IV trimethoprim: 7.9 ± 3.2 B: IV sulfamethoxazole: 186.4 ± 59.9 B, PO trimethoprim: 8.3 ± 3.3 B: PO sulfamethoxazole: 181.8 ± 74.7	• Not discussed	• Dosage adjustment does not appear necessary when switching from IV to PO • Only 4 critically ill patients and 8 non-critically ill patients were evaluated for oral administration PK • No significant difference in AUC was observed between IV and PO doses • In critically ill patients, a switch from IV to PO trimethoprim-sulfamethoxazole may be feasible when tolerating oral feeds (good F observed), but the evidence is based on data from only 4 patients.
Antifungals											

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Buijk et al.[4] (42), 2001	Prospective Observational	Fluconazole 400 mg IV Q24H One additional 400 mg IV dose after 12 hours on day 1 Day 4: 400 mg via feeding tube (if clinical condition allowed)	Critically ill abdominal surgery patients in the ICU	14 All received IV, 10 received oral, and data from 1 was excluded	71	53 (45-61)	124 (90-158)	AUC (mg*h/L) IV: 409 (336-482) Enteral: 418 (319-516)	C_{max} (mg/L) IV: 24.7 (21.7-27.8) Enteral: 20.4 (16.5-24.2)	• Short bowel	• Concentrations of fluconazole were adequate to treat most cases of deep mycoses in this group • Bioavailability was reported very high in 3 patients, likely due to increased clearance with IV dosing compared to enteral dosing • Fluconazole efficacy best determined by AUC/MIC. Data showed AUCs high enough to treat *Candida* infections with MIC of 16 mg/L
Nicolau et al.[5], 1995	Prospective Observational	Fluconazole 100 or 200 mg once daily IV or enteral, eligible for switch to alternate route after 5 doses	Critically ill patients requiring fluconazole Continuous or bolus TF. Feeds held temporarily for drug administration if continuous TF	Total: 7 2 excluded from analysis (incom-plete sampling) 5/7 patients received enteral doses	100	45 (22-69)	Entire population: 84.7 ± 18.6 After excluding 2 patients with recent rifampicin dosing (N=5): 97.2 ± 9.8	AUC (mg*h/L) Population average NR Range, IV: 74.4-428.1 Range, TF: 68.1-470.9	C_{max} (mg/L) Population average NR Range, IV: 5.17-20.99 Range, TF: 3.43-22.62	• Not discussed	• Fluconazole had excellent enteral bioavailability in critically ill patients when given via feeding tube • Data from patients who received rifampin was excluded as the results were likely skewed by the microsomal enzyme-inducing effects of rifampin
Pelz et al.[6], 2002	Prospective Interventional	Fluconazole Loading Dose: 800 mg (all patients) Maintenance Dose: 400 mg daily If creatinine clearance <25	Critically ill surgical patients in the ICU. Fluconazole used for prophylaxis A: Fluconazole, PO, NG, or NJ B: Placebo	A: 121 B: 130	57	63 (20-92)	NR	NR	C random (µg/mL) A, median: 11.9 (0-69.8)	• No significant differences in concentration seen with route of administration (gastric, oral, or jejunostomy) • No significant differences in concentration seen with history of surgery Yes/No	• Enteral administration resulted in serum levels above MIC for >2/3 of *Candida* isolates • Authors have concluded that enteral fluconazole is adequate for preventing more *Candida* infections in critically ill surgical patients.

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
		mL/min, maintenance dose: 200 mg daily (22% of group A got this dose)									
Karoubi et al.[7], 2016 (abstract)	Prospective Observational	Voriconazole Loading Dose: 6 mg/kg IV Q12H for 2 doses Maintenance Dose: 5 mg/kg IV Q12H Day 4 on: 5 mg/kg Q12H through NG tube	Critically ill patients on mechanical ventilation Continuous TF	8	63	67.5 (49-86)	106 (77-135)	NR	C_{max} (mg/L) IV: 5.8 ± 2.0 NG: 10.2 ± 4.2	• Not discussed	• Data suggests a switch to NG voriconazole after initial IV therapy could be used • TDM recommended to avoid potential toxicity supratherapeutic concentrations seen in 4 patients
Antivirals											
Mulla et al.[8], 2013	Prospective Observational	Oseltamivir Enteral, 75 mg BID Administered by NG tube	Critically ill adult patients with H1N1 influenza (suspected or confirmed) receiving ECMO support	14	57	38.8 ± 7.42	Oseltamivir 25 Oseltamivir carboxylate 75	Median AUC (ng/h/mL) oseltamivir carboxylate 4346 (644-13660)	Median C_{max} (ng/mL) oseltamivir carboxylate 509 (54-1277)	• Variability in PO bioavailability suspected to be from decreased gut motility and impaired gut perfusion as expected in critically ill patients	• Mean exposure of oseltamivir carboxylate (active metabolite) in critically ill ECMO patients was comparable to ambulatory patients (data from another study)

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Taylor et al.[9], 2008	Case Series	Oseltamivir 150 mg BID x10 days	Mechanically ventilated patients NG drug administration	3	33	Patient A: 30 Patient B: 22 Patient C: 76	NR	AUC_{0-12} (ng*h/mL) Oseltamivir Phosphate A: 395 B: 1059 C: 628 Oseltamivir Carboxylate A: 5,932 B: 10,951 C: 34,670	C_{max} (ng/mL) Oseltamivir Phosphate A: 122 B: 156 C: 28.7 Oseltamivir Carboxylate A: 591 B: 1210 C: 1270	• Not discussed	• Double dose oseltamivir with NG administration was absorbed well in these patients • High AUC values likely due to reduced renal function in the patients • 2 patients died, possibly due to late treatment and advanced disease at presentation
Tomlin et al.[10], 2010 (abstract)	Case Study	Oseltamivir 75 mg BID NG Dose doubled after no response seen	Young adult female with H1N1 infection	1	0	NR	NR	NR	Oseltamivir phosphate: 10-77 ng/mL Oseltamivir carboxylate: 2,600-5,000 ng/mL	• Not discussed	• Elevated oseltamivir carboxylate levels possibly due to reduced renal elimination • Absorption did not appear to be affected
GASTRIC ACID SUPPRESSING MEDICATIONS											

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Pemberton et al.[11], 1993	Prospective Interventional	Ranitidine, NG administration A: 150 mg q12h B: 300 mg q12h	Postoperative or posttraumatic surgical patients in the ICU NG tubes clamped for 1 h after administration	18 A: 10 B: 8	 A: 60 B: 50	 A: 44.6 ± 18.2 B: 51.9 ± 21.6	NR	NR	Mean serum concentration (ng/mL) T = 2 h A: 298.02 ± 198.69 B: 639.84 ± 282.92 T = 6 h A: 221.09 ± 164.43 B: 473.90 ± 259.31 T = 12 h A: 98.68 ± 68.31 B: 316.66 ± 28.72	• Tube feeds held after drug administration	• Enteral administration of ranitidine led to effective absorption in ICU patients • Both doses provided serum concentrations high enough to suppress gastric acid production
Other Medications											
DeCarolis et al.[12], 2016	Retrospective Observational	Potassium chloride Mean IV Dose: 30.5 ± 14.7 mmol Mean Enteral Dose: 35.5 ± 18.8 mmol	All patients in ICU and SICU receiving the study drug between Dec 2007 and Apr 2008 Max 5 unique doses per patient	142 patients 16 got IV and enteral IV: 109 Patients, 212 Doses Enteral: 49 patients, 66 Doses	IV: 99 Enteral: 94	IV: 66.9 ± 12.9 Enteral: 64.2 ± 11.2	NR	NR	Change in plasma potassium (mmol/L) IV: 0.25 (0.16 to 0.33) Enteral: 0.27 (0.15 to 9.39)	• Not discussed	• No difference in mean dose response after IV or enteral administration was observed • Overall success of reaching the minimum potassium concentration defined by each protocol was 61% for IV and 59% for enteral administration • Using IV over enteral route for potassium administration did not appear to offer any advantage

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Main findings and clinical considerations
Murray et al.[13], 1998	Prospective Interventional	Tacrolimus All patients received study drug with both regimens Doses ranged from 1-8 mg BID	Transplant patients at least 7 days after surgery Regimens: A: TF held 1 hr prior to and 8 hr after drug administration B: Continuous TF	10	60	Mean 53 (29-67)	NR	Dose-normalized AUC (ng/mL/h/mg) A: 26.8 ± 10.7 B: 25.2 ± 12.3	C_{min} (ng/mL) A: 1-13.0 B: 5-12 C_{max} (ng/mL) A: 5-46 B: 5.2-36.3	• Possible interaction with TF	• Participants received Osmolite® • Administration of tacrolimus with TF did not appear to interfere with drug absorption
Shalansky et al.[14], 1992	Prospective Interventional	Aminophylline Dose: to target serum concentration 10-20 mg/L	Critically ill, mechanically ventilated patients Phase 1: IV aminophylline Phase 2: Aminophylline liquid through NG or gastronomy tube Continuous TF	8	38	Mean 63 (57-69)	103 ± 22	AUC_{0-8} (units not provided) range IV: 67.37-117.79 NG: 66.87-120.15	Mean serum concentration range (mg/L) IV: 8.4-14/7 8.3-14.7 NG:	• Possible interaction with TF	• Near 100% oral bioavailability was observed • No reduction in absorption was observed with coadministration of aminophylline and the feed formulas (Isocan®, Osmolite ®, and Magnacal®)
Sharpe et al.[15], 2013	Prospective Interventional	Thyroxine 2 µg/kg PO or IV All patients received a PO and IV drug, one of which was placebo	Solid organ donors in the ICU A: Thyroxine PO B: Thyroxine IV	32 A: 15 B: 17	 A: 87 B: 47	 A: 61 ± 14 B: 53 ± 17	91-93	AUC Average (pmol*hr/L) A: 86.1 B: 92.2 Difference: 6.1, 95% CI -11.9 to 24.1, P=0.52	NR	• Not discussed	• It appears that thyroxine is well absorbed in organ donors in the ICU

ECMO: extracorporeal membrane oxygenation support; AUC, area under curve; BMT, bone marrow transplant; C, concentration; F; bioavailability; IV, intravenous; N, number of participants in the study; NICU, Neonatal Intensive Care Unit; NR, not reported, PICU, Pediatric Intensive Care Unit; PK, pharmacokinetics; PO; per oral.

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Bioavailability of Orally Administered Drugs in Critically Ill Patients

Supplementary Table 3. Summarizing table of all articles discussing altered drug absorption in pediatrics.

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Clinical implications

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Clinical implications
Arenas-Lopez et al.[1], 2014	Prospective observational	Clonidine 3 µg/kg, single dose	A population PK-model was conducted on post-cardiac surgical patients at the PICU comparing results to healthy patients from another study Drug administration via NG	16	NR	6.7 months (5.9-8.6)	NR	NR	C_{max} (ng/ml) 0.73 (0.15-1.55) with T_{max} (min) 190 (12-478)	• Reduced splenic blood flow due to cardiac surgery • Clonidine solution was not diluted	• The majority reached therapeutic drug concentrations • Slow absorption rate. T_{max} in healthy subjects: 63 min • High inter-individual variability in C_{max}
Kleiber et al.[2], 2019	Prospective observational	Acetaminophen 15 mg/kg IV q6h Single dose microtracer [^{14}C] Acetaminophen at 3 ng/kg	A populations PK-model on patients managed at PICU [^{14}C]-marked drug Enteral dose given concurrently with IV dose	47	80.9	6.1 months (1.8-20)	72 (11-91)	NR	C_{ss} (mg/L): PO: 6.5 IV: 10	• Use of opioids	• C_{ss} subtherapeutic after PO • C_{ss} extrapolated from data from single dose of enteral microtracer acetaminophen • Risk of therapy failure with enteral administration
Marsot et al.[3], 2014	Retrospective observational	Phenobarbital IV or PO: 10-20 mg/kg loading dose, followed by 5 mg/kg	A population PK-model was conducted on patients managed at the NICU Data collection for both IV and PO administration Average weight was between 0.7-10 kg	48	60	Gestational (week): 37.1 ± 3.3 Postnatal (days): 26.8 ± 64.0	48.9	NR	Random (mg/L): PO: 23.2 ± 10.4 IV: 27.1 ± 9.4	• Phenobarbital is a weak acid. The gastric pH is higher in neonates compared with adults	• TDM is necessary in this population • May need high loading and maintenance doses for oral administration
Williams et al.[4], 2019 (abstract)	Retrospective observational	Phenobarbital Dose: NR	A population PK-model was conducted on patients managed at the NICU	112	NR	NR	85	NR	NR	NR	• Higher bioavailability than previously reported, but still lower than implied (100%)
Matthias et al.[5], 2012	Case report	Posaconazole Day 55-60: 100 mg TID increased to 600 mg q6h Day 61-174: 400 mg q4h Day 175-387: 800 mg q6h	Case 1 Patient, 19.1 kg, suffered from leukemia and had undergone a BMT Day 55-60: NG Day 61-174: NG Day 175-387: PO Day 175-230: bolus feeding with drug administration Day 52-225: concomitant parenteral nutrition	1	100	10	NR	NR	Random (µg/ml): Day 55-60: <0.15 Day 61-174: NR Day 175-229: 0.32-0.78 Day 230-387: <0.3, often undetectable	• Interaction with PPI • Interactions with other drugs • Interactions with the TF formula • Inconsistent rate of enteral nutrition (case 2)	• Both patients received higher doses than recommended without significant adverse effects • Both cases experienced subtherapeutic serum posaconazole concentrations

Author, year	Study type	Drug and dose	Study population	N	Sex (% Male)	Age (years)	F (%)	AUC	C	Factors altering drug absorption	Clinical implications
			Day 231-387: continuous TF PPI prophylaxis treatment								
		Posaconazole Day 46-59: 120-300 mg/kg/day divided q4h Day 60-100: 3000 mg/day Day 101-134: 1500 mg/day	Case 2 BMT patient, 11.6 kg, with a history of seizures and leukemia Day 46-59: jejunostomy tube. TF held for two h after drug administration Day 60-134: jejunostomy tube. Continuous oral infusion Day 135: discontinued therapy Day 1-156: enteral nutrition Day 1-66, 91-108 and 135-156: parenteral nutrition PPI prophylaxis treatment	1	100	19 months	NR	NR	Random (µg/ml): Day 46-59: <0.20 Day 60-100: 0.36-0.85 Day 101-134: 0.2		
Miles et al.[6], 1990	Prospective Observational	Carbamazepine <12y: 10 mg/kg loading dose ≥12y: 8 mg/kg loading dose	PICU patients with frequent seizures Doses given through feeding tube 1 patient received enteral feeds	6	67	5 (0.2-13.9)			Mean C (mg/L), excluding patient with ileus 1 h after dose: 4.3 2 h after dose: 7.3 8 h after: 6.2	• Ileus (one patient did not reach therapeutic concentrations because of it) • Delayed gastric emptying • Enteral feeds	• All patients excluding one with an ileus had therapeutic concentrations 2 hours after loading dose administration • 4 patients had therapeutic concentrations at 1 hour and 6 hours after loading dose administration • Enteral feeds in one patient appeared to delay, but not reduce, absorption. • Enteral carbamazepine in this population appears appropriate without dosage adjustment. • Avoiding enteral feeds may be appropriate if rapid effect is required

AUC, area under curve; BMT, bone marrow transplant; C, concentration; F; bioavailability; IV, intravenous; N, number of participants in the study; NICU, Neonatal Intensive Care Unit; NR, not reported, PICU, Pediatric Intensive Care Unit; PK, pharmacokinetics; PO; per oral.

Supplementary Table 3 References

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