Online Supplement

Definitions
Shock: Shock was defined as the need for treatment with norepinephrine ≥5 μg/minute (or an equivalent dose of another vasopressor) for 4 hours or more, provided that at least 30 ml/kilogram body weight of crystalloid or an equivalent volume of colloid was administered during the 8-hour interval surrounding the start of vasopressor treatment. \(^1\)

Impaired kidney function: The EXTRIP nephrology sub-committee defined impaired kidney function, from the perspective of poison clearance, to include \(^2\) 1) Advanced stage G3b, G4 or G5 chronic kidney disease (i.e. eGFR < 45 mL/min/1.73 m\(^2\)), 2) KDIGO Stage 2 or 3 acute kidney injury, 3) In the absence of a baseline serum creatinine, 2 mg/dL (176 µmol/L) in adults and 1.5 mg/dl (132 µmol/L) in elderly/low muscle mass patients, 4) in children with no baseline creatinine, a serum creatinine greater than twice the upper limit of normal for age and gender, 5) the presence of oligo/anuria, regardless of serum creatinine concentration. It was decided not to separate acute and chronic kidney impairment because such a distinction did not appear to be meaningful for this purpose.

Hepatic failure: The American Association for the Study of Liver Disease definition of acute liver failure includes the presence of coagulation abnormality as evidence with an INR > 1.5 and alteration of mental status with any degree of encephalopathy in a patient without any prior evidence of liver disease and an illness less than 26 weeks \(^3\). The definition of hyper acute or fulminant liver failure with duration of less than 7 days is also mentioned. There are no routinely available biochemical tests for further grading of liver function that are analogous to various stages of creatinine concentration for renal function. However, the presence of cirrhosis and ascites is associated with a prolonged half-life of various medications, including those that are predominantly cleared by kidneys (e.g., antibiotics \(^4\)), so the same effect may occur with metformin. Hepatic failure will also impair the endogenous clearance of lactic acid.

Acknowledgements
We would like to acknowledge the tremendous work of our dedicated translators: Marcela Covica, Alexandra Angulo, Ania Gresziak, Monique Cormier, Samantha Challinor, Martine Blanchet, Gunel Alpman, Joshua Pepper, Lee Anderson, Andreas Betz, Tetsuya Yamada, Nathalie Eeckhout, Matthew Fisher, Ruth Morton, Denise Gemmellaro, Nadia Bracq, Olga Bogatova, Sana Ahmed, Christiane Frasca, Katalin Fenyvesi, Timothy Durgin,
Helen Johnson, Martha Oswald, Ewa Brodziuk, David Young, Akiko Burns, Anna Lautzenheiser, Banumathy Sridharan, Charlotte Robert, Liliana Ionescu, Lucile Mckay, Vilma Etchart, Valentina Bartoli, Nathan Weatherdon, Marcia Neff, Margit Tischler, Sarah Michel, Simona Vairo, Mairi Arbuckle, Luc Ranger, Nerissa Lowe, Angelina White, Salih Topal, John Hartmann, Karine Mardini, Mahala Bartle Mathiassen, Anant Vipat, Gregory Shapiro, Hannele Marttila, Kapka Lazorova. We also acknowledge the important contribution from our librarians and secretarial aids: Marc Lamarre, David Soteros, Salih Topal, Henry Gaston, and Brenda Gallant.
Table S1: Scoring the quality of evidence for kinetic outcomes (individual studies)

<table>
<thead>
<tr>
<th>Quality of evidence score</th>
<th>Interpretation and application to individual studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Sufficient PK data present; % removed is reported or can be calculated; reported calculations are appropriate.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Sufficient PK data present, but % removed is NOT reported or CANNOT be calculated; reported calculations (e.g., ( CL_{EC}/CL_{TOT} )) are appropriate.</td>
</tr>
<tr>
<td>Low</td>
<td>Sufficient PK parameters may be reported, but supporting data absent or suspect, reported calculations inappropriate, or other serious limitations exist.</td>
</tr>
<tr>
<td>Very Low</td>
<td>Sufficient PK parameters and supporting data not adequately reported, questionable or no calculations reported. However, based on theoretical knowledge of ( V_D ), protein binding, ( CL_{SYS} ), molecular weight, etc, some assumptions can be made about dialyzability.</td>
</tr>
<tr>
<td>Reject</td>
<td>Questionable parameters reported with no supporting data, fatal flaw in study design.</td>
</tr>
</tbody>
</table>
Figure S1: Grading of dialyzability as a function of ECTR and endogenous clearance

Endogenous metformin clearance was estimated by 4x CrCL, metformin clearance by IHD was based on the maximum reported of 200 mL/min\(^5\), while metformin clearance by CRRT was based on 50 mL/min\(^6,7\).

This figure illustrates that dialyzability criteria (based on clearance) depends on both endogenous clearance (which depends on creatinine clearance) and ECTR clearance. For example, if a patient has a creatinine clearance of 30 mL/min and undergoes CRRT, metformin will only be “slightly dialyzable”. For the same patient that undergoes HD, metformin would be expected to be moderately dialyzable. Alternatively, if the creatinine clearance is 120 mL/min, CRRT will at best augment total body clearance of only 10% (i.e. not dialyzable).

REFERENCES

