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Aggressive Early Crystalloid Resuscitation adversely affects Outcomes in Adult Blunt Trauma Patients: An Analysis of the Glue Grant Database

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Abstract

Background—Evidence suggests that aggressive crystalloid resuscitation is associated with significant morbidity in various clinical settings. We wanted to assess whether aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients.

Methods—Data were derived from the Glue Grant database. Our primary outcome measure was all-cause in-hospital mortality. Secondary outcomes included days on mechanical ventilation; intensive care unit (ICU) and hospital length of stay (LOS); inflammatory - (acute lung injury and respiratory distress syndrome [ALI/ARDS], multiple organ failure [MOF]) and resuscitation-related morbidity (abdominal and extremity compartment syndromes, acute renal failure) and nosocomial infections (ventilator associated pneumonia [VAP], bloodstream [BSI], urinary tract [UTI] and surgical site infections [SSI]).

Results—In our sample of 1,754 patients, in-hospital mortality was not affected, but ventilator days ($p<0.001$), as well as ICU ($p=0.009$) and hospital ($p=0.002$) LOS correlated strongly with the amount of crystalloids infused in the first 24 hours post-injury. Amount of crystalloid resuscitation was also associated with development of ARDS ($p<0.001$), MOF ($p<0.001$), bloodstream ($p=0.001$) and SSI ($p<0.001$), as well as abdominal ($p<0.001$) and extremity compartment syndromes ($p=0.028$) in a dose-dependent fashion, when age, Glasgow Coma Scale (GCS) severity of injury and acute physiologic derangement, comorbidities, and colloid & blood product transfusions were controlled for.

Conclusion—Crystalloid resuscitation is associated with a substantial increase in morbidity, as well as ICU and hospital LOS in adult blunt trauma patients.

Level of Evidence—2b

Background

Despite significant advances in medical science have led to major breakthroughs against disease and unprecedented life expectancy and quality of life and over the past few decades, resuscitation science has failed to keep pace and the fluids most commonly used, namely

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normal saline and lactated ringer's solution, have been used with little change since they were first introduced in the 19th century. (1, 2) Similarly, aggressive resuscitative strategies, that have constituted the cornerstone of early trauma management for decades, had not been challenged until recently, when data obtained in a prospective randomized fashion on patients with penetrating torso injuries suggested that restrictive resuscitation might improve morbidity and mortality, (3) raising the question that perhaps resuscitative fluids themselves conferred additional morbidity. Since time-honored trauma resuscitation strategies were brought back into question, evidence has been mounting that liberal crystalloid administration may be associated with adverse clinical outcomes in the pediatric, (4-6) burn, (7) neurosurgical, (8) critically ill, (9) and the blunt trauma population. (10, 11) The common denominator across these references is that the aggressive crystalloid resuscitation, likely due to the worsening of acidosis, (12-14) local endothelial disruption, (15) and volume overload it confers, (9) triggers an inflammatory response (16-19) that substantially increases morbidity.

With the current project we aim to establish whether an association exists between clinically relevant outcomes and volume of crystalloid resuscitation in adult blunt trauma patients.

Methods

Data Collection

Data were extracted from a prospectively collected multicenter cohort of severely injured blunt trauma patients in hemorrhagic shock, the Glue Grant initiative (National Institute of Medical Sciences, Inflammation and the Host Response to Injury Collaborative Program, www.gluegrant.com). Enrolment criteria for the Glue Grant study include a blunt mechanism of injury, an abbreviated injury score (AIS) ≥ 2 in any body region excluding the brain, and significant hemorrhage requiring blood product transfusion within 12 hours (h) of injury or manifesting as prehospital or emergency department (ED) hypotension (systolic blood pressure <90 mmHg) or an elevated base deficit (BD) ≥ 6 meq/L. Trauma victims younger than 16 or older than 90 years were excluded, and so were those with spinal cord injury, isolated brain trauma and thermal burns $>20\%$ of total body surface area. An extensive dataset was collected prospectively in all cohort subjects that were able to provide informed consent either directly, or through a healthcare proxy over the course of 8 years. These data include demographics, mechanism and severity of injury, pre-existing comorbid conditions, overall fluid and blood product resuscitation parameters, serial laboratories and multiple clinically relevant outcomes. Standardized protocols were developed and implemented across all participating institutions to minimize variability in post-injury care, including for initial trauma fluid and blood product resuscitation; mechanical ventilation and weaning; ICU insulin infusion; venous thromboembolism prophylaxis; and sedation and analgesia as indicated. (20) After compilation and validation, de-identified data were included in the Glue Grant investigator-accessible database for secondary analyses. Data collection was approved by the regional institutional review boards (IRB) of all participating centers, and secondary analysis presented here by the Partners Healthcare IRB.

Definition of Complications

During the enrolled subjects' stay in the ICU, multiple organ dysfunction scores for renal, hepatic, cardiovascular, metabolic, respiratory and neurologic systems were determined daily and the diagnosis of multiple organ system failure (MOF) required a Marshall Multiple Organ Dysfunction score >5 (21). Definitions of the outcomes of interest in the Glue Grant cohort, namely acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), abdominal and extremity compartment syndromes, acute renal failure, ventilator associated

pneumonia (VAP), bloodstream (BSI), urinary tract (UTI) and surgical site infections (SSI) have been described extensively elsewhere. (22)

Hypothesis

Our primary hypothesis was that volume of crystalloid resuscitation received in the first 24h post-injury does not affect in-hospital mortality. Secondary outcomes included commonly used clinically relevant outcome measures, such as time on mechanical ventilation; ICU and hospital LOS; inflammatory (ALI/ARDS, MOF) and resuscitation-related morbidity (abdominal and extremity compartment syndrome, acute renal failure) and nosocomial infections (VAP, BSI, UTI and SSI).

Analysis

Total volumes of crystalloid, colloid and blood product (packed red blood cells [PRBC] and fresh frozen plasma [FFP]) resuscitation were calculated for the first 24h post-injury, as resuscitative efforts were complete within this timeframe in the overwhelming majority of patients. To simplify analysis and interpretation of results, blood product volumes were translated from the raw data from milliliters (mL) to average volumes of standard component therapy in units (U) per the following conversion scheme: 1 U of PRBC = 350 mL; 1 U FFP= 250 mL. Multivariate logistic and linear regression analyses of our binary and continuous outcome measures were performed respectively, controlling for age, scene Glasgow Coma Scale (GCS), (23) Injury Severity (24) and APACHE II (25) scores, comorbidities (using a Charlson comorbidity index (26)), colloid and blood product (PRBC & FFP U) administration over the same time frame. Using a Kernel density distribution for the 24h crystalloid resuscitation, we divided our sample population in four clinically relevant and easily memorable volume groups and performed analysis of variance for the outcome measures, where crystalloid resuscitation was found to be an independent predictor for. Adjusted Odds Ratios were subsequently calculated for the binary outcomes for which 24h volume of crystalloid resuscitation had been identified as a predictor for, after controlling for the aforementioned confounders.

Results

From November 2003 to October 2011, a total of 2,002 blunt trauma victims were enrolled across all participating trauma centers nationwide. For our analysis we excluded trauma victims that expired within 48 h or were discharged home within 72 h to exclude those with irreversible hemorrhagic shock and non-survivable trauma, as well as those with minor injury burden. Adolescents younger than 18 years and victims with a combined penetrating mechanism were also excluded for a total sample size of 1,754 (figure 1), the characteristics of whom are summarized on table 1. Overall, our sample comprised fairly young (mean age 43.5 ± 18) and otherwise healthy patients – 90% of the entire cohort had a Charlson comorbidity index of 0 or 1. As expected from the inclusion criteria, injury acuity was very high, with 72% of the cohort having an ISS greater than 25. Systolic blood pressure averaged around 109, but base deficit and lactate levels were significantly deranged, -8.4 and 4.4 on average respectively.

From our multivariable regression model, amount of crystalloid resuscitation administered in the first 24h post-injury was not found to be an independent predictor of all-cause mortality, our primary outcome, therefore we could not reject our null hypothesis. (table 2). Not surprisingly, older age ($p<0.001$), poorer neurologic status (lower scene Glasgow Coma Scale, $p=0.031$), and more severe injury (greater Injury Severity Scores, $p=0.001$) and acute physiologic derangement (higher APACHE II scores, $p<0.001$) were independently associated with higher mortality. Volume of crystalloid resuscitation was also found to be a

predictor for number of days on mechanical ventilation ($p<0.001$), and also the ICU ($p=0.009$) and hospital ($p=0.002$) length of stay (table 2). An association was also noted between volume of crystalloids given and development of ALI/ARDS ($p<0.001$), MOF ($p<0.001$), abdominal ($p<0.001$) and extremity ($p=0.028$) compartment syndromes, and surprisingly enough, bloodstream ($p=0.001$) and surgical site infections ($p<0.001$).

To reach clinically meaningful and memorable conclusions from our study, we divided our cohort in 5L volume subgroups and made comparisons between these groups. The baseline characteristics and incidence of complications across these volume groups are summarized on table 3.

To avoid confounding from age and pre-existing comorbidities, neurologic status, injury and physiologic derangement burden, and colloid and blood product administration, we controlled for those factors in our regression model and calculated the adjusted Odds Ratios (OR) for the binary outcomes we identified crystalloid resuscitation to be a predictor for. Volume of crystalloid resuscitation was noted to be associated with the development of ALI/ARDS, MOF, abdominal compartment syndrome and SSI in a dose-dependent fashion (table 4).

Patients who received >15 L of crystalloids in the first 24h post-injury had 3 times the odds of developing ALI/ARDS (adjusted OR 3.4 (1.5–7.9), $p<0.005$), MOF (adjusted OR 2.9 (1.3–6.1), $p<0.007$), or SSI (adjusted OR 2.8 (1–8.2), $p<0.005$) (table 4, figure 2) compared to their counterparts who received less than 5 L of crystalloids in the first 24h post-injury. The increase in risk was even more dramatic in the development of abdominal compartment syndrome, as those who received between 10–15 L of crystalloid resuscitation had 5 times the odds of developing this complication compared to the 5–10 L group. The risk increased to almost 9 in patients that received >15 L of crystalloids.

Discussion

Despite ongoing advances in resuscitative medicine, the determination of the optimal methods and goals of resuscitation remain elusive and an area of intense controversy. (27, 28) As the concept of ‘damage control resuscitation’ has slowly but steadily grown in popularity over the past decade and a half, it has become increasingly clear that while immediate and aggressive fluid resuscitation of the injured victim may rapidly improve the vital signs of both patient and treating physician, the overall effect on outcome may be much less comforting. (27, 29, 30) The physician in charge of the resuscitation efforts must remain mindful of the post-traumatic and dilutional coagulopathy (10, 31, 32), iatrogenic volume overload (9, 33), and the myriad complications stemming from the physiologic and immunologic effects of large volume resuscitation and massive blood product transfusion strategies. (16, 17, 19, 27, 30, 34).

As a growing body of evidence points to significant morbidity associated with even moderate volumes of crystalloid (4) or blood component therapy (27, 35) in a variety of clinical settings, we aimed to determine the effect of crystalloid resuscitation on clinically relevant outcomes and complications in adult blunt trauma victims, the most frequent recipient population of such resuscitation efforts. While we did not find an association between volume of crystalloid resuscitation and mortality, our primary outcome measure, significant associations were noted between crystalloid volume infused during the first post-injury day and highly morbid complications, such as ALI/ARDS, MOF, abdominal and extremity compartment syndromes, and even infectious complications, notably bloodstream and surgical site infections, that we believe will form the first step toward abandoning overly aggressive resuscitation protocols from trauma practices worldwide. We were not able to

identify an association between crystalloid volume and mortality even when we included all deaths in our exploratory analysis, as early mortality was noted to be related mainly to injury burden, and not resuscitation. However, all remaining associations became stronger as the denominator decreased - patients still alive at 48 hours (one would have to be alive to develop a complication).

While associative relationships between resuscitative components and adverse outcomes have been previously described, (27, 33, 36-40) controversy persists over whether these relationships constituted a mere surrogate for injury severity or represented a truly causative effect. In other words, what has so far been unclear is whether sicker patients with greater injury burden went on to develop various complications as a result of their trauma-induced physiologic derangements, and not due to the massive resuscitation they received. To answer that question, we controlled for both injury severity and acute physiologic derangement, as well as preexisting comorbidities, age and neurologic status, all well-recognized markers of unfavorable outcomes. We also controlled for colloid and blood component administration, as those have been recently associated with adverse outcomes in trauma victims.

We elected to use the multi-institutional Glue Grant cohort for our secondary analysis, as we believe it represents the most accurate, extensive and well-validated prospectively collected dataset for the population of interest. In contrast to previously published efforts that have used 12h resuscitation volumes, (27) we elected to analyze resuscitation administered over the first 24h. The rationale behind this decision was to ensure that acute resuscitation is complete and would be more indicative of future fluid-related complications, should such associations be identified, as a 12h window would be too narrow for such determinations, as frequently resuscitation is still ongoing, especially in the case of distant pre-hospital transfers or lengthy surgical interventions. We also elected to omit platelet transfusions from our analysis, as the majority of the Glue Grant cohort did not receive any platelet component therapy, and the majority of those who did, received only one unit. We also wanted to maintain power in our regression model to the extent possible, ensuring inclusion of well-recognized confounders associated with adverse outcomes, as well as other more commonly used blood component therapy, so their effect would be controlled for in our analysis. A separate outcomes analysis associated with blood component therapy in the blunt trauma population is currently under way.

After dividing our cohort into four distinct crystalloid volume groups so we could arrive at more meaningful and clinically memorable conclusions, we noted some differences between the baseline characteristics across the four groups. Interestingly enough, age and comorbidities appeared to be lower in the higher volume resuscitation groups, while severity of neurologic injury (scene GCS) remained fairly constant across resuscitation groups. And although injury severity and acute physiology scores rose – as expected – across the four groups, the differences only in the latter reached statistical significance in our analysis of variance (table 3). Also, even though base deficit appeared to be significantly higher in the larger volume groups, the differences were not necessarily clinically significant (BD difference between the <5 L and the > 15 L groups was 2 points).

While the major difference in the baseline characteristics across the various volume groups was noted in APACHE II, ventilator days, ICU and hospital LOS were significantly higher in the subgroups that received larger crystalloid volumes (table 3). Dramatic increases were also noted in the incidence of ALI/ARDS, MOF, compartment syndromes and BSI and SSI in the higher volume groups, and these differences did reach statistical significance on analysis of variance. Interestingly, even after controlling for the aforementioned confounders, the incidence of ALI/ARDS and MOF was significantly higher in the higher

volume groups, as was that of abdominal compartment syndrome, a complication well recognized to be tightly associated with higher resuscitation volumes. In fact, the Odds Ratio for development of ALI/ARDS and MOF was three times higher in the >15 L volume group, even after adjusting for severity of injury and physiologic derangement, as well as blood component therapy, likely suggesting a causative mechanism. It is likely the highly acidic nature of the fluids most commonly used in acute trauma resuscitation (normal saline and lactated ringer's) trigger a dose-dependent acute inflammatory response that, not dissimilarly from other highly inflammatory conditions known to be associated with ALI/ARDS and MOF, may easily affect the pulmonary parenchyma as it spirals out of control. (16-19) It is also possible that vascular overdilatation from volume overload accentuates this phenomenon from local endothelial damage unrelated to the original traumatic insult. (15)

Not surprisingly, incidence of abdominal compartment syndrome rose dramatically in the higher volume groups, while extremity compartment syndrome lost significance in our controlled analysis, suggesting that for the development of the latter, voluminous fluid resuscitation must act synergistically with a primary local injury for the clinical syndrome to develop, unlike the case of abdominal compartment syndrome, where high volumes alone may lead to this extremely morbid complication.

One of the most intriguing findings in our study was the higher incidence of surgical site and bloodstream infections in the larger crystalloid volume groups, even though the latter barely missed statistical significance ($p=0.056$) in our adjusted analysis. The incidence of the former rose from 8% and 4.6% respectively to 20.9% with higher volumes of resuscitation, for an adjusted Odds Ratio of nearly 3 in the subgroup that received >15L of crystalloids. Perhaps, higher volumes of resuscitation bear a previously unrecognized immunomodulatory, or even immunocompromising effect that renders the body less capable of fighting infectious insults. It is interesting, however, that the elevated risk for infectious complications did not translate to significantly higher risk for VAP. Not surprisingly, the number of UTIs (13-15%) and the incidence of ARF (0-2%) remained rather stable across volume groups, as larger fluid volumes improved filtration rates and bestowed a protective effect on the kidneys.

Despite the use of statistical models to the best of our ability to adjust for injury severity, baseline patient characteristics and concomitant resuscitation with blood products, to fully account for the complex interactions between injury and outcome and the medical interventions in-between, as previously described by Klein et al remains challenging. (7) However, we believe this is a firm attempt at demonstrating the potential adverse outcomes excessive fluid resuscitation may confer, as these complex interactions will continue to be in place, and urge the medical community with the privilege to care for the injured to refrain from it, until well-designed randomized studies shed more light on the optimal method and goals of resuscitation and help develop optimal resuscitation strategies and protocols.

Conclusion

High volume of crystalloid resuscitation confers prolonged time on the ventilator, ICU and hospital length of stay in the adult blunt trauma population. It also appears to be associated in a dose-dependent fashion with a substantial increase in highly morbid complications, such as ALI/ARDS, MOF, abdominal compartment syndrome and surgical site infections, even when baseline patient characteristics, trauma burden and blood product transfusions are controlled for. The current guidelines for crystalloid resuscitation in adult blunt trauma warrant revisiting.

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Figure 1.
Flow diagram of determination of our study population.

Figure 2. Adjusted Odds Ratios for the development of ALI or ARDS, MOF, abdominal compartment syndrome and SSI across the four 24h crystalloid resuscitations volume groups.

Table 1

Demographics and characteristics of our sample population (SD: Standard deviation; ED: Emergency department; SBP: Systolic blood pressure; HR: Heart rate; GCS: Scene Glasgow Coma Scale; WBC: White blood cell count; Hb: Hemoglobin; BD: Base deficit; APACHE II: Acute Physiology and Chronic Health Evaluation II Score; ISS: Injury Severity Score; ICU: Intensive Care Unit; LOS: Length of stay)

	Mean $\pm$ SD	Range
Age (yr)	43.5 $\pm$ 18.0	18 - 90
Male sex (%)	66.6%	
ED SBP (mmHg)	111.1 $\pm$ 30.6	0 – 243
ED HR (min ⁻¹)	109.0 $\pm$ 26.7	0 – 200
GCS	11.3 $\pm$ 4.6	3 – 15
WBC	16.6 $\pm$ 7.7	1 – 50.8
Hb (g/dL)	11.5 $\pm$ 2.5	2.7 – 18.7
BD	(- 8.4) $\pm$ 4.5	(-30) – 11
Lactate (mmol/L)	4.4 $\pm$ 2.6	0.6 – 25
APACHE II	28.1 $\pm$ 7.2	5 – 49
ISS	32.2 $\pm$ 13.4	1 – 75
ISS>25 (%)	71.7	
Charlson Comorbidity Index	0.4 $\pm$ 1.0	0 – 10
Major surgery in 1 st 24h (%)	33.4	
Ventilator days (d)	10.4 $\pm$ 10.8	0 – 135
ICU LOS (d)	14.0 $\pm$ 12.6	0 – 142
Hospital LOS (d)	25.1 $\pm$ 22.8	3 – 354
Mortality (%)	9.1	

Table 2

Effect of 24h crystalloid resuscitation on our outcome measures when age, admission GCS, injury and acute physiology severity, pre-existing comorbidities and colloid and blood product resuscitation were controlled for (ICU: Intensive Care Unit; LOS: Length of stay; ALI/ARDS: Acute Lung Injury and Acute Respiratory Distress Syndrome; ARF: Acute renal failure; MOF: Multiple organ failure; VAP: Ventilator-associated pneumonia; UTI: Urinary tract infection; BSI: Bloodstream infection; SSI: Surgical site infection)

Outcome	<i>p</i>-value
Mortality	0.275
Ventilator days	<0.001
ICU LOS	0.009
Hospital LOS	0.002
ALI/ARDS	<0.001
ARF	0.407
MOF	<0.001
Abdominal compartment syndrome	<0.001
Extremity compartment syndrome	0.028
VAP	0.135
UTI	0.324
BSI	0.001
SSI	<0.001

Table 3

Distribution of injury severity across crystalloid volume strata and dose-dependent effect of crystalloid resuscitation on morbidity, presented as means and standard deviations. (GCS: Scene Glasgow Coma Scale; ED: Emergency department; SBP: Systolic blood pressure; HR: Heart rate; ISS: Injury Severity Score; APACHE II: Acute Physiology and Chronic Health Evaluation II Score; ICU: Intensive Care Unit; LOS: Length of stay; ALI/ARDS: Acute Lung Injury and Acute Respiratory Distress Syndrome; MOF: Multiple organ failure; BSI: Bloodstream infection; SSI: Surgical site infection)

24-h crystalloid resuscitation	<5 L	5-10 L	10-15 L	>15 L	p-value
N=	87	475	574	618	
Age	50.9 ± 21.4	44.9 ± 19	43.4 ± 17.3	41.5 ± 17.1	0.004
GCS	11.1 ± 4.9	11.6 ± 4.4	11.3 ± 4.6	11.0 ± 4.8	0.332
ED SBP (mmHg)	106 ± 32.8	108 ± 27.5	111 ± 31.5	113 ± 31.5	0.014
ED HR (min ⁻¹)	103.2 ± 26.7	104.1 ± 25.9	109.5 ± 26.4	113.3 ± 27	0.807
BD (	(-7) ± 5	(-7) ± 4.3	(-8) ± 4.1	(-9) ± 4.6	<0.001
Hb (g/dL)	11.4 ± 2.5	11.6 ± 2.3	11.5 ± 2.5	11.3 ± 2.8	0.105
ISS	27.8 ± 12.9	29.9 ± 12.6	32.1 ± 13.6	34.8 ± 13.4	0.348
Apache II	23.9 ± 8	26.1 ± 7.6	27.6 ± 6.8	30.6 ± 6.2	<0.001
Comorbidity index	0.6 ± 1.4	0.5 ± 1.1	0.4 ± 0.9	0.3 ± 0.9	<0.001
Ventilator days	7.3 ± 7.9	8.4 ± 9.2	10 ± 11.4	12.8 ± 11.2	<0.001
ICU LOS	11.3 ± 8.7	12.5 ± 12.1	13.1 ± 12.2	16.4 ± 13.6	<0.001
Hospital LOS	19.6 ± 12.2	21.6 ± 19.5	23.8 ± 17.7	30 ± 29.1	<0.001
ALI/ARDS (%)	11.5	14.1	23.3	37.5	<0.001
MOF (%)	14.9	20.2	28.2	46.4	<0.001
Abd. comp. synd. (%)	0	0.6	4.3	12.1	<0.001
Extremity comp. synd. (%)	1.1	1.7	3.6	5.7	0.003
BSI (%)	8	9.9	12.9	20.9	<0.001
SSI (%)	4.6	9.1	14.1	20.9	<0.001

Adjusted Odds Ratios for the binary outcomes for which volume of crystalloid resuscitation in the first 24h after injury was identified to be a predictor of. (Odds Ratios controlled for age, Glasgow Coma Scale, Injury Severity and APACHE II scores, comorbidities, colloid and blood product administration over the same time frame) (O.R.: Odds Ratios; 95% C.I.: 95% confidence intervals; ALI/ARDS: Acute Lung Injury and Acute Respiratory Distress Syndrome; MOF: Multiple organ failure; BSI: Bloodstream infection; SSI: Surgical site infection)

Table 4

	<5 L	5-10 L	5-10 L	5-10 L	>15 L
	O.R. (95% C.I.)	p	O.R. (95% C.I.)	p	O.R. (95% C.I.)
ALI/ARDS	reference	1.7 (0.71-3.9)	0.24	2.3 (1.5-4)	0.05
MOF	reference	1.5 (0.7-3.3)	0.29	1.9 (0.9-4.1)	0.1
Abd comp synd	n/a	reference	4.8 (1.4-16.4)	0.01	8.7 (2.6-28.9)
Extr comp synd	reference	1.3 (0.2-10.5)	0.835	2.4 (0.3-18.9)	0.393
BSI	reference	1.5 (0.6-4)	0.398	1.9 (0.7-4.8)	0.206
SSI	reference	1.7 (0.6-5)	0.32	2.3 (0.8-6.6)	0.12
					2.8 (1-8.2)
					0.05