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1	Aspirin and Anti-Platelet Agents, Statins, and Beta-blockers					
	Cardiac Troponin Measurement in the Critically Ill: Potential for Guiding Clinical Management	**Poe /2015/25**	Retrospective cohort	Critically-ill Veterans in cTn cohort without other cardiac diagnosis n=19,979	30 day mortality with high cTn, OR 1.82 (95% CI 1.62, 2.04) P= <0.001; On BB OR 0.81 (95% CI 0.68,0.95) P=0.009; On Statin OR 0.99 (95% CI 0.82,1.19) P=0.9105; On Aspirin OR 0.81 (95% CI 0.69,0.96) P=0.0165	Is elevated cTn level associated with 30-day mortality, and are there additional associations with ASA, statin, or beta blocker use in critically-ill veterans?
	Aspirin and Anti-Platelet agents					
2	Prehospital statin and aspirin use and the prevalence of severe sepsis and acute lung injury/acute respiratory distress syndrome	**O'Neal/2011/30**	Prospective cohort, cross-sectional analysis	575 MICU or SICU patients aspirin and statin	Multivariate analysis, statin prehospital less likely to develop severe sepsis (OR 0.62, 0.40-0.96) or ALI/ARDS (OR 0.60, 0.36-0.99) in 1st 4 days. No change in hospital mortality. Prehospital ASA and statin use had lowest severe sepsis, ALI/ARDS.	Is prehospital ASA and statin use associated with lower risk of sepsis, ALI, or ARDS?
3	Antiplatelet therapy is associated with decreased transfusion-associated risk of lung dysfunction,	**Harr/2013/31**	Secondary analysis of prospective Glue Grant.	839 severely injured blunt trauma patients, excluded TBI	Pre-injury antiplatelet associated with less lung dysfunction(p=0.0116), multi-organ failure (p=0.0291), and trend to reduced	Is antiplatelet use (ASA, clopidogrel, or ticlopidine) associated with reduced ALI, MOF, or mortality?

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	multiple organ failure, and mortality in trauma patients				mortality(p=0.06)	
4	Association of prehospitalization aspirin therapy and acute lung injury: results of a multicenter international observational study of at-risk patients	**Kor/2011/32**	Secondary analysis of prospective cohort study with propensity scoring	Patients at risk for acute lung injury; 3,855, 976 on ASA	Univariate analysis suggests reduced ALI in ASA patients (OR 0.65, 0.46-0.90, p=0.01). After propensity adjustment, no association with prehospital ASA and ALI (OR 0.70, 0.48-1.03, p=0.72).	Is prehospital ASA associated with reduced risk in patients at risk for acute lung injury?
5	Outcomes of severe sepsis and septic shock patients on chronic antiplatelet treatment: a historical cohort study	**Valerio-Rojas/2013/33**	Retrospective cohort with propensity analysis	Severe sepsis, septic shock; 651 patients, 43% on aspirin	After adjusting, no reduction in mortality with ASA (OR 0.73, 0.46-1.16), ALI and ARDS was reduced (OR 0.62, 0.45-0.87).	Is prehospital ASA associated with reduced ALI/ARDS or mortality?
6	Prehospitalization antiplatelet therapy is associated with a reduced incidence of acute lung injury: a population-based cohort study	**Erlich/2011/34**	Retrospective cohort 2006, at risk for ALI with propensity score	161 MICU patients at risk for ALI in 2006	ASA associated with reduced incidence ALI/ARDS (OR 0.37, 0.16-0.84, p=0.02), after adjustment.	Is prehospital ASA associated with reduced ALI?
7	Prehospital aspirin use is associated with reduced risk of acute respiratory distress syndrome in	**Chen/2015/35**	Secondary analysis of prospective study with propensity score	1,149 critically ill patients	After adjusting, prehospital ASA associated with reduced ARDS (OR 0.66, 0.46-0.94)	Is prehospital ASA associated with less ARDS?

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	critically ill patients: a propensity-adjusted analysis					
8	Acetyl salicylic acid usage and mortality in critically ill patients with the systemic inflammatory response syndrome and sepsis	**Eisen/2012/36**	Retrospective cohort with propensity analysis	All consecutive ICU admissions (7,945) from 4/2000-11/2009; 5,523 first episode of SIRS, 2,082 given ASA	ASA associated with lower mortality in sepsis patients after propensity matching (27.4% vs 42.2%, absolute RR 14.8% (18.9%, 8.6%)	Does ASA reduce mortality in SIRS patients?
9	Effects of low-dose acetylsalicylic acid and atherosclerotic vascular diseases on the outcome in patients with severe sepsis or septic shock	**Otto/2013/37**	Retrospective chart review, logistic regression but no propensity analysis	886 septic patients to SICU	ASA: lower mortality (OR 0.56, 0.37-0.84) Statin: no mortality benefit Clopidogrel had similar benefit to ASA, but if ASA and clopidogrel together – benefit was lost	Is ASA or statin associated with reduced mortality in septic patients?
10	Benefit of low-dose aspirin and non-steroidal anti-inflammatory drugs in septic patients	**Sossdorf/2013/39**	Retrospective chart review	979 severe sepsis patients	ASA associated with lower mortality OR 0.57, 0.39-0.83); NSAID also benefit OR 0.5, 0.26-0.94; benefit abolished when given together OR 1.12, 0.55-2.25	Are NSAIDs also associated with lower mortality in septic patients?
11	Aspirin Has a Protective Effect Against Adverse Outcomes in Patients with Nonvariceal Upper	**Wehbeh/2015/40**	Retrospective review	ICU patients with upper GI bleeding; 717 patients with non-variceal UGIB, 56% taking	Multivariate analysis, ASA is protective against in hospital mortality OR 0.26, 0.13-0.53	Determine the effect of ASA on mortality in patients with non-variceal upper GI bleeding?

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	Gastrointestinal Bleeding			at least 1 antithrombotic agent		
12	Antiplatelet drugs and outcome in mixed admissions to an intensive care unit	**Winning/2010/41**	Retrospective cohort	615 mixed medical-surgical patients	Logistic regression analysis showed pre-admit antiplatelet agents associated with reduced mortality (OR 0.19, 0.12-0.33), especially if APACHE II > 20	Hypothesis: antiplatelet drugs favorably affect outcome in patients non-electively admitted to an intensive care unit.
13	Association between aspirin therapy and the outcome in critically ill patients: a nested cohort study	**Al Harbi/2016/42**	Nested cohort of two combined RCTs (one RCT – insulin regimen, other – feeding regimen)	763 ICU patients	ASA is not associated with reduced mortality adjusted OR 1.18, 0.69-2.02, p=0.55; ASA was associated with increased risk of severe sepsis and increased mechanical ventilation duration	Is antiplatelet therapy associated with reduced mortality in an ICU population?
	Statins					
14	Effect of statin therapy on mortality in patients with ventilator-associated pneumonia: a randomized clinical trial	**Papazian/2013/45**	RCT double blinded multicenter	ICU patients requiring mechanical ventilation APACHE 18-19 (Anticipated mortality 27-30%)	No significant difference in mortality in statin treated patients with SUSPECTED ventilator assisted pneumonia. Stopped early for futility (300 patients enrolled of anticipated 1,002 patients)	To determine whether statin therapy reduces 28-day mortality in patients with ventilator assisted pneumonia
15	Rosuvastatin for sepsis-associated	**Truwit/2014/46**	RCT double blinded	745 ICU patients with ARDS;	No difference in mortality in either group.	To determine whether rosuvastatin (40mg load,

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	acute respiratory distress syndrome		multicenter	stopped for futility APACHE III 99 (one third, or APACHE II 22.5) 42% death rate	Increased risk of hepatic and renal adverse effects.	20mg daily) reduced hospital or 60-day mortality in sepsis related ARDS patients
16	Simvastatin in the acute respiratory distress syndrome	**McAuley/2014/47**	RCT double blinded multicenter	ICU patients with ARDS, 540 patients enrolled APACHE II 18-19	No difference (including 20-day mortality) in statin treated group, also no difference in adverse effects.	Does simvastatin 80mg improve ventilator free days in patients?
17	A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis	**Kruger/2013/48**	Phase II, RCT double blinded multicenter	ICU patients with severe sepsis; 250 randomized, APACHE II 22-25	Acute use of atorvastatin does not alter IL-6 levels, but trend toward improved 28-day mortality in patients who had been on statin prior to study and were kept on it (mortality higher in group where it was stopped)	Does atorvastatin 20mg alter IL-6 concentration, ICU mortality or 28 and 90-day mortality?
18	Impact of statins in outcomes of septic patients: a systematic review	**Tralhao/2014/49**	Systematic review	RCTs and cohort studies of statins in sepsis	5 RCTs do not show mortality benefit from statins in sepsis patients; 16 cohort studies showed benefit	Meta-analysis of statins in sepsis, and whether there is mortality benefit?
19	Statin therapy in critically-ill patients with severe sepsis: a review and meta-analysis of randomized clinical	**Thomas/2015/50**	Meta-analysis	4 RCTs in critically ill patients with sepsis, 1818 patients	4 RCTs, sepsis; no difference in 28-day mortality (RR 0.953, 0.715-1.271) or 60-day mortality (RR 0.93, 0.722-1.198)	Meta-analysis of statins in critically-ill septic patients, is there mortality benefit?

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	trials					
20	The effect of statins on mortality in septic patients: a meta-analysis of randomized controlled trials	**Pasin/2013/51**	Meta-analysis	RCTs statins in septic patients, 650 patients, 5 RCTs	No difference in mortality with statins (RR 0.90, 0.65-1.26, p=0.6)	Meta-analysis of statins in sepsis, and whether there is mortality benefit?
21	Statin therapy and mortality from sepsis: a meta-analysis of randomized trials	**Deshpande/2015/52**	Meta-analysis and systematic review	Septic patients; 7 RCTs, 1,720 patients	No reduction in-hospital mortality (RR 1.04, 0.87-1.24, p=0.68) or 28-day mortality (RR 0.93, 0.46-1.89, p=0.85)	Is there mortality benefit from statins in septic patients?
22	Safety and vasopressor effect of rosuvastatin in septic patients	**El Gendy/2014/53**	RCT, blinded, single center	108 septic patients, APACHE 24-25	No difference in ICU and in-hospital mortality, significantly improved number of acceptable BP and SP days with statin (11=/-3 vs. 8 +/- 3 (p=0.0001)	Does statin improve number of acceptable BP and systemic perfusion days (primary) or mortality (secondary)?
23	Randomized double-blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (ASEPSIS Trial)	**Patel/2012/54**	RCT, blinded, single center	100 non-ICU septic patients, APACHE II score 12 (14.6% anticipated mortality)	Atorva associated with significantly reduced conversion to severe sepsis (4% vs 24%, p-0.007); no difference in mortality, no differences in adverse effects.	Does atorvastatin 40mg reduce sepsis progression in statin naïve patients hospitalized with sepsis?
	Beta blockers					
24	Effect of heart rate control with esmolol	**Morelli/2013/55**	Prospective, open-label,	Septic shock requiring	Intervention: IV esmolol to keep HR 80-94 bpm	To investigate the effect of short acting esmolol in

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	on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial		randomized, controlled phase 2 clinical trial	norephinephrine to maintain BP to MAP 65mmHg	for 96 hours Outcome: 28 day mortality HR 0.39, 95% CI 0.26-0.59, p<0.001	patients with severe septic shock
25	Early Propranolol after Traumatic Brain Injury is Associated with Lower Mortality	**Ko/2016/61**	Prospective non-randomized (selected by ICU and neurosurgical attendings)	440 moderate to severe traumatic brain injury patients in ICU (propranolol started 5 hours after admission, 15 doses)	Propranolol TBI compared to patients not given propranolol; multivariate analysis showed lower mortality in propranolol group OR 0.25, 95% CI 0.08-0.74, p=0.012	Does early propranolol administration reduce mortality in TBI patients?
26	Traumatic Brain Injury and beta-blockers: Not All Drugs Are Created Equal	**Schroeppel/2014/62**	Retrospective, multivariable adjusted	1,755 TBI patients in ICU	No mortality benefit from BB alone with adjusted analysis, however propranolol vs all other BB showed benefit (3% vs 15% mortality, p=0.002, adjusted OR 0.199, 95% CI 0.043-0.92)	Hypothesis: propranolol is the best beta-blocker to block excess catecholamines and improve mortality in this population.
27	Prospective evaluation of early propranolol after traumatic brain injury	**Murry/2016/63**	Prospective observational; administered propranolol, not randomized	Moderate to severe TBI in ICU; 38 patients (28 with propranolol, 10 without (but could get other BB)	Intervention: propranolol in first 24 hours of admission, continued 48 hours. Outcome: Mortality rates similar (10% vs 10.7%, p=0.9), but severity of injury was significantly worse in the	Will Propranolol be associated with improved outcomes in moderate and severe TBI patients?

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					non-propranolol group (80% non-propranolol group still got other BB)	
28	Beta-adrenergic blockade and traumatic brain injury: protective?	**Schroeppel/2010/64**	Retrospective chart review	Blunt TBI patients 2,601, >1 dose BB (506, 20%)	Multivariate analysis, BB protective OR 0.347 (95% CI 0.246-0.490)	Does suppression of catecholamine surge in TBI reduce mortality?
29	Beta-blocker exposure in patients with severe traumatic brain injury (TBI) and cardiac uncoupling	**Riordan/2007/65**	Retrospective review with propensity analysis	Severe TBI in 4,116 patients, 141 with BB (29%).	Cardiac uncoupling= reduction in HRV in the first 24 hours post-TBI; BB exposure associated with reduced mortality among all patients with severe TBI, regardless of degree of cardiac uncoupling.	Does BB reduce mortality in severe TBI patients? How does this relate to cardiac uncoupling?
30	Beta-blockers in isolated blunt head injury	**Inaba/2008/66**	Retrospective review	Isolated TBI patients 1,156, 203 (18% on BB)	Stepwise logistic regression: BB is an independent protective factor for mortality aOR 0.54 (95% CI 0.33-0.91, p=0.01) Elderly and more severely injured (abbreviated injury score >/= 4) had even better outcomes OR 0.3 (0.1-0.6, p=0.001)	Are BB associated with improved survival in acute TBI patients?
31	Beta-blocker exposure is associated with improved survival after severe	**Cotton/2007/67**	Retrospective review with propensity scoring, BB exposure = 2 or	TBI patients (severity (AIS) of 3 or greater; BB group older, more severely	420 patients, 174 patients exposed. aOR with propensity score analysis 0.29 (95% CI 0.14-0.60, p=0.001)	Does adrenergic blockade improve survival among TBI patients?

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	traumatic brain injury		more days	injured, lower predicted survival.		
32	Beta-blocker use is associated with improved outcomes in adult trauma pts.	**Arbabi/2007/68**	Retrospective cohort, MV analysis	4,117 Trauma patients, 303 (7%) on BB. 45% on BB pre-injury.	OR for mortality in BB group was 0.3 (p<0.001) for BB cohort compared to control.	To determine the safety of BB in head injury patients.
33	Troponin increases in the critically injured patient: mechanical trauma or physiologic stress?	**Martin/2005/4**	Retrospective review	All trauma patients with cTn levels	1,081 patients, mortality significantly elevated in cTn increased patients (29%): Any increase in cTn was a strong independent predictor of mortality aOR 2.1 (1.4-3.1). BB use assc with 50% decrease in mortality among patients with elevated cTn (38% vs 16%, p<0.01).	What are the etiologic factors and prognostic significance of increased cTn levels in a widely screened trauma population?
34	Beta-blocker Exposure in the absence of significant head injuries is associated with reduced mortality in critically ill patients.	**Bukur/2012/69**	Retrospective with multivariable analysis	Critically ill trauma patients without severe TBI, 663 patients	aOR 0.37 (95% CI 0.18-0.76), p=0.007; BB are an independent protective factor for mortality, not protective in pts less severely injured (injury severity score < 25) aOR 1.42 (95% CI 0.85-2.36) p=0.181	To determine the impact of beta-blocker exposure on mortality in critically injured trauma patients who did not sustain significant head injuries.
35	Preadmission beta-blocker use and 30-day mortality among patients in	**Christensen/2011/70**	Retrospective analysis with propensity matching,	All ICU patients older than 45, 8,087 total, 3,112 after propensity	30-day mortality 25.7% users vs 31.4% non-users (OR 0.74, 0.63-0.87), surgical patients 0.69	What is the association between beta-blocker use in 30-day mortality of ICU patients?

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	intensive care: a cohort study		preadmission beta-blockers	matching (1,556 in each group)	(0.54-0.88), medical 0.71 (0.51-0.98), cardioselective bb 0.70 (0.58-0.83), non-selective 0.99 (0.67-1.47)	
36	The safety of beta-blocker use in chronic obstructive pulmonary disease patients with respiratory failure in the intensive care unit	**Kargin/2014/71**	Retrospective case-control, APACHE (19-20) **would have anticipated benefit from ASA also – no mention of ASA use in this group**	188 acute respiratory failure with COPD in ICU	Mortality in ICU 17.6% vs 15.8% ($p > 0.75$) In-hospital 18.9% vs 19.3% ($p>0.95$) 30-days post-discharge 20% vs 11% ($p>0.47$) – no difference in mortality between groups **when used for HR control**.	To compare BB to non-BB rate lowering drugs in COPD patients with acute respiratory failure "due to heart rate limiting" with respect to mortality