439. Pros and cons of MDR- and XDR-TB treatment

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Outcomes for multidrug-resistant tuberculosis patients with and without resistance to fluoroquinolones and second-line injectable drugs: A meta-analysis of individual patient data

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Poor treatment outcomes have been reported for tuberculosis (TB) patients harbouring strains resistant to isoniazid and rifampicin (multidrug resistance or MDR-TB), fluoroquinolones and/or second-line injectable drugs.
We undertook a meta-analysis for response to treatment using individual data for MDR-TB patients whose strains had additional resistance to fluoroquinolones (MDR-TB+FQ), second-line injectables (MDR-TB+Inj) or both (extensive drug resistance; XDR-TB) including demographic and clinical details, treatment regimens, and outcomes.
26 centres provided data for 424 MDR-TB+FQ, 1129 MDR-TB+Inj, 405 XDR-TB, and 4776 other MDR-TB patients susceptible to FQ and Inj. Success was lower in MDR-TB+FQ (adjusted OR=0.6 [95%CL 0.5-0.7]) and XDR-TB patients (0.4 [0.3-0.6]) than in those with MDR-TB+Inj (0.8 [0.7-0.9]) and those with MDR-TB and no additional resistance (reference). No single drug was significantly associated with treatment success in MDR-TB+FQ and XDR-TB patients. In XDR-TB patients, success was highest if at least 6 drugs were used in the intensive phase (4.9 [1.4-16.6]) and 4 in the continuation phase (6.1[1.4-26.3]).
Study results suggest that regimens of a similar duration to those recommended in MDR-TB patients but containing more drugs achieve better results in XDR-TB patients. As all data in the analysis were from observational studies, bias may be substantial and better quality evidence will be needed to guide the optimization of regimens.

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Treatment outcomes of extensively-drug resistant tuberculosis (XDR-TB) patients in 20 countries

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Background: Tuberculosis patients who are resistant to rifampicin, isoniazid, fluoroquinolones and second-line injectable drugs present a serious challenge to TB treatment programmes. In 2006, the World Health Organization (WHO) started surveillance for this condition, defined as extensive drug resistance (XDR-TB). We describe outcomes of XDR-TB patients started on treatment in 2008.
Methods: We used the latest data reported by countries to WHO by December 2011. Treatment regimens were known to differ between countries. Standardized definitions for outcomes were widely applied.
Results: 20 countries reported outcomes for a total of 641 XDR-TB cases. Most cases were reported by South Africa (345), Peru (70), Romania (53), Georgia (49), Brazil (45) and Namibia (20), with other countries reporting a median of two cases each (range 1-19). Overall treatment success was 23%, 34% of cases died, 22% failed treatment, 12% defaulted and 9% were not evaluated. Success of 50% or more was only achieved by countries managing 1-3 cases. In countries with >20 cases, deaths were highest in Namibia (90%) and South Africa (40%), and failures peaked in Brazil (80%) and Romania (55%). More than half the cases in Peru were either not evaluated or defaulted.
Conclusions: National data reported to WHO show less favourable outcomes for XDR-TB patients than have, to date, been published in the literature, and are similar to untreated tuberculosis. The high mortality in southern African countries may be associated with HIV co-morbidity and low access to anti-retroviral agents. Better optimization of regimens and support to potential defaulters is recommended.

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Culture conversion rates of multi-drug resistant (MDR-TB) patients treated in the community versus an inpatient setting in a rural area of the Western Cape (WC) of South Africa

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Introduction: The MDR programme to theWest Coast Winelands area consists of inpatient treatment centres and an outreach programme, for treatment of patients in the community.
Objective: To compare baseline demographic and culture conversion rates among patients initiating MDR-TB treatment in the community versus those initiated as inpatients.
Methods: We retrospectively reviewed clinical records at the inpatient Centre of patients diagnosed between 2000 – 2006 with a first episode of MDR-TB. Patients were included if started on a regimen with 3 or more second-line anti-TB drugs (SLD), came from this area and had a bacteriological confirmed diagnosis. Time from diagnosis to treatment initiation and from initiation to culture conversion were determined, and demographic and clinical indicators at baseline.
Results: 502 patients were diagnosed with new MDR-TB, among which 324 (64.5%) started on SLD. Median age was 34, with 105 females (32%). 145/324 (45%) started in the community vs. 179 (55%) as inpatients. Inpatients and community-based were similar in baseline age and AFB result; but inpatients were more likely to be female (40% v. 23%; p<0.01), and had lower weights (47.3kg v. 53.3kg; p<0.01). Inpatients had a longer time to treatment initiation (76 v. 64 days; p<0.01). Of 172/324(53.1%) who converted, 96 (54%) were inpatients and 76/145(52%) community-based. Days to conversion were also similar between the two groups: community 121 (IQR 61-206.5) and inpatient 105 (IQR 64.5-164).
Conclusion: Algorithms are needed for identifying patients suitable for treatment in the community.

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DOTS PLUS versus non DOTS PLUS outcomes in MDRTB patients

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Romania is confronted with an important number of MDRTB cases.
2007, DOTS PLUS strategy was applied in the management of selected MDRTB cases.
Aim: To assess the impact of DOTS PLUS strategy on cases registered in Iasi, Romania in 2007-2010.
Method: Comparative analysis of MDRTB characteristics, treatment regimens and outcomes in 2 groups of MDRTB patients; first with 21 cases treated using DOTS PLUS strategy, second: 48 cases not included in DOTS PLUS cohort.
Results: First group (9F/12M) 11 new TB cases, 10 relapses.
Second group (11F/37M) 20 new TB cases, 25 relapses, 2 treatments after default, 1 chronic, previously treated with second line drugs.
First group received treatment according to WHO guidelines, with 6-7 drugs: Z, E,1 injectable, Ofx, Pto, Cs, PAS.
Second group received individualized treatment depending on intermittent drug supply of different aminoglicosides and fluoroquinolones, without PAS.
Median number of doses for injectable drugs was 196 in DOTS PLUS group/102 in the second group and of 330 doses/225 doses for Ofloxacin.
There were significant differences between number of doses both in fluoroquinolones and aminoglicosides (p<0.003).
Final treatment outcomes: success 57.1% in DOTS PLUS group/31.2% in the second group and death rate 9.5% versus 35.4%.
Comparative analysis revealed significant differences regarding success rate (p<0.05) and death rate (p=0.02).
Conclusions: Treatment outcomes in DOTS PLUS group were significantly better; Weak points in the non DOTS PLUS group were identified (e.g: insufficient doses of injectable drugs);
DOTS PLUS ensures both correct regimens with access to all active second line drugs and regular drug supply; it is an opportunity for proper management of MDRTB cases.

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Aminoglycoside ototoxicity monitoring in multidrug resistant tuberculosis: How much is enough?

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Background: There is no widely accepted protocol to monitor for potentially irreversible ototoxicity in aminoglycoside treated patients with multidrug resistant tuberculosis (MDR-TB). Experience suggested that we should perform audiometric assessments every 2-4 weeks when using these drugs. This is a more intensive protocol than generally described.
Aim: To evaluate the use of frequent audiometric assessments in MDR-TB patients receiving extended-duration aminoglycosides and to describe their influence on subsequent clinical management.
Methods: Retrospective review of audiometrical and clinical records of MDR-TB patients treated with amikacin at single site London MDR TB service 2009-2011. Hearing loss was graded using the NCI criteria recommended by the American Academy of Audiologists.
Results: 12 patients were assessed. The median dose of amikacin received was 98.3 grams (IQR, 80.8-111.2) over a median period of 122 (92-144) days. Patients had a median of 8.5 (5.5-10) audiograms at 2.3 weekly intervals. 3 (25%) developed grade 1 hearing loss during amikacin therapy at a median time of 116 (95-148) days. All progressed to grade 2 or 3 loss after treatment cessation. 9 (75%) stopped amikacin treatment earlier than originally planned due to audiological complaints (8 with significant tinnitus and 4 with abnormal audiograms).
Conclusion: Aminoglycoside associated ototoxicity appears common despite frequent audiological assessments and often leads to early treatment discontinuation. Other ototoxic agents should be avoided if possible. The optimal type and fre-

quency of audiometric assessments need to be determined within a prospective study.
VM & HW are joint first authors.

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Adverse effects of moxifloxacin during tuberculosis treatment
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Aim: Prolonged use of moxifloxacin in tuberculosis (TB) may have adverse effects, particularly prolongation of the QT interval and arrhythmias.
Methods: All TB patients treated with moxifloxacin from 2003-2011 were identified. Concurrent medication and history of drug abuse were noted. Charts noted adverse effects. ECGs were obtained on and off treatment and the longest QTc was used for the study.
Results: 93 patients treated with moxifloxacin for at least one month were identified. Adverse effects included: nausea (2), palpitations (1) and photosensitivity (1); itching, arthralgia, flushing amd depression were probably due to concurrent medication. 60 patients had ECGs, mostly taken during treatment and none had a QTc >500 ms. Variability in QTc was high (standard deviation 31 ms). One male had a QTc > 450 and 3 females >470 ms but none had arrhythmias; one patient developed right bundle branch block during treatment, but this persisted when not taking moxifloxacin. All 4 used opiates.

Code	Sex	Pre-treatment QTc's (ms)	QTc's during treatment (ms)
8.078	M	441, 424, 444, 476	430, 472, 479
6.104	F	421, 446, 451, 456,460, 471, 475	456, 475, 479
9.045	F	413, 439, 460, 482	456
9.129	F	404, 409, 438, 450, 480	373, 426, 429, 429, 439, 480, 492

28 patients had paired ECGs on and off treatment showing a QTc interval increase of 6,4 msec (95% CI -4,2 to 17,0 msec). Five increased by 69, 51, 48, 44 and 40 ms of whom four had limited access to opiates while in prison during their pre-treatment ECGs. Only one of the 28 had a QTc >450 ms after a normal interval (413 to 482 ms).
Conclusions: Moxifloxacin is well tolerated in treating TB. ECGs should be performed at a standard time after ingestion and with concurrent urine drug screens.

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Adverse reactions during treatment of multidrug-resistant and extensively drug-resistant tuberculosis
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Introduction: Treatment of multidrug-resistant tuberculosis (MDR-TB) and extensively resistant tuberculosis (XDR-TB) is often complicated by adverse reactions.
Objectives: To describe the adverse reactions, time of occurrence, attitudes and risk factors among MDR/XDR-TB patients.
Methods: Retrospective cohort of all patients with MDR/XDR-TB evaluated at the Regional Referral Center for MDR/XDR-TB in northern Portugal from July 2009 until January 2012.
Results: We analyzed 29 patients, 19 (65.5%) men, mean age 48 years. Eighteen (62.1%) had co-morbidities of which HIV infection was the most frequent (8 patients). Twenty-two patients (75.9%) had adverse reactions and 17 (77.3%) had to suspend the drug involved. Median time to occurrence of adverse reactions was 94 days (min=2, max=619). Toxicity related to the injectable drug was the most frequent - 9 (31%) with ototoxicity, and 7 (24.1%) with renal insufficiency. Hypothyroidism was present in 6 (20.7%) of the patients. Psychiatric disorders, associated to cicloserine occurred in 6 (20.7%) patients. Multivariate analysis could not identify independent risk factors in relation to adverse reactions. The occurrence of adverse reactions was not associated with a higher risk of dead or a worse outcome.
Conclusions: The occurrence of adverse reactions more often correlated with the injectable drug and occurred around the third month. We could not identify independent risk factors for adverse reactions and they did not affect the outcome.

440. Acute exacerbation in COPD

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Short term glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: "REDUCE*", a non-inferiority multicenter trial. (*Reduction in the Use of Corticosteroids in Exacerbated COPD; ISRCTN19646069)
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Background: The optimal dose and duration of systemic glucocorticoid therapy for acute exacerbations of COPD (AECOPD) is unknown. In this trial, we aimed to demonstrate non-inferiority of 5-days vs 14-days of systemic glucocorticoids with respect to COPD exacerbation.
Methods: Patients admitted to hospital with AECOPD were randomized to receive 40mg of prednisone-equivalent daily for either 5 or 14 days in a placebo-controlled fashion. Follow-up was 180 days. The primary endpoint was time to next exacerbation.
Results: Of 721 evaluated patients, 327 underwent randomization, and 304 completed the study. Mean age was 63.9±23.2 years; mean FEV1%predicted 31.5±14.3% and 60.8% were male. Exacerbations occurred in 36.8% and 38.4% of patients in the 5 day and 14 day treatment arms, respectively (p=0.81). Time to exacerbation did not differ between groups in the intention-to-treat and per-protocol analyses (hazard ratios for the short treatment arm, 0.92 [95%-CI, 0.64 to 1.34; p=0.67] and 0.91 [95%-CI, 0.63 to 1.32; p=0.62], respectively); nor did time to death or the combined endpoint of exacerbation and/or death, with both hazard ratios for the short treatment arm being <1 as well. With respect to the primary outcome, short treatment was not inferior to conventional treatment, since the 95%-confidence intervals did not include the predefined non-inferiority threshold of 1.515.
Conclusion: In AECOPD, 5-day treatment with systemic glucocorticoids is non-inferior to 14-day treatment with regard to re-exacerbation during 6 months of follow-up.

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Relationship between exacerbation frequency and survival post MI in COPD patients
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COPD patients are at increased risk of myocardial infarction (MI),1 particularly after an exacerbation.2 COPD patients have shorter survival after MI compared to the general population. We investigated whether COPD patients with frequent exacerbations (FE) had shorter survival post MI than patients with infrequent exacerbations (IE).
All COPD patients with a first MI between 1/1/03 and 31/12/08 as recorded in MINAP, who had no previous evidence of MI in GPRD or MINAP were included. Patients under 35, not registered with GPRD at the time of MI, or with less than 1 year of follow-up before their MI were excluded. Exacerbations were defined using pre-defined READ codes and prescription of pre-specified antibiotics and/or steroids. FE had ≥2 exacerbations in the year preceding MI and IE <2. Data were provided by the CALIBER group at UCL. The primary outcome was death after MI. Cox proportional hazards models were used to adjust for potential confounders. 1063 patients were identified with a first STEMI or NSTEMI. 111 (10.4%) FE and 952 (89.6%) IE. The unadjusted mortality rate in FE was 285.7 deaths (95%CI 222.3-367.2) per 1000 person years and in IE 152.4 deaths (95% CI 138.1-168.1) per 1000 person years. Adjusting for confounding by smoking and gender and stratifying by age, mortality was greater in FE compared to IE; HR 1.61(95%CI 1.23-2.11);p=0.001. Mortality was greater in patients who exacerbated in the 2 months preceding the MI; HR 3.88(2.70-5.56):p<0.001.
Conclusions: FE have shorter survival after a first MI than IE. There appears to be an association between timing of exacerbations, exacerbation frequency and survival after 1st MI.

References:
[1] Feary et al Thorax 2011.
[2] Donaldson et al Chest 2010.

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The impact of airway infection on cardiovascular risk during COPD exacerbations

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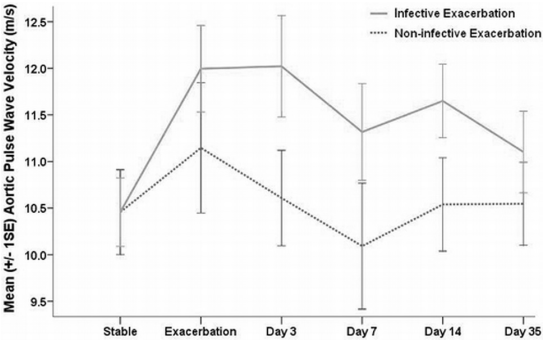
Arterial stiffness, a validated measure of cardiovascular risk, increases from stable COPD to exacerbation (Patel et al, ERS 2011). We hypothesised this increased cardiovascular risk was mediated by airway infection.
We measured aortic pulse wave velocity (aPWV) in the stable state, at exacerbation and during recovery at 3,7,14 and 35days thereafter. Infective exacerbations were defined by a potentially pathogenic microbe (PPM) in exacerbation sputum by culture or positive PCR for *H. influenzae, S. pneumoniae, M. catarrhalis*, or human rhinovirus. Differences in the area under the curve (AUC) adjusted for stable aPWV level between groups were compared by unpaired t-test.
55 COPD patients (32 male, 11 current smokers) had a mean±SD FEV_1 of 1.14±0.41L (46.7±18.5%predicted) and FEV_1/FVC ratio 0.46±0.14. Two-thirds of them (36/55, 65%) produced a sputum sample at exacerbation. Two-thirds of these events (24/36, 67%) had an identifiable PPM. Patients with an infective exacerbation had a greater rise in arterial stiffness from stable state to exacerbation (1.4±1.7ms-1 vs 0.4±1.0ms-1, p=0.050). Arterial stiffness was also higher during the recovery period in those with an infective exacerbation (AUC 37.4±55.2ms-1days vs 11.4±44.3ms-1days, p=0.036).



The increase in arterial stiffness during COPD exacerbations appears to be driven by airway infection and may explain the association between these infective events and increased cardiovascular risk.

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Evaluation of multiple admissions of COPD patients: European COPD audit

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Background: Patients with multiple admissions represent an especially at risk population with therapeutic and prognostic implications. The European COPD Audit is a clinical audit to evaluate clinical practice variability, clinical and organisational factors related to outcomes for COPD admissions across Europe (422 hospitals from 13 European countries). The present communication aimed at evaluating multiple admission patients and their clinical features and outcomes.
Methods: The study comprised a first 8-week phase during which all consecutive cases admitted to hospital due to an exacerbation of COPD were identified and information on clinical practice and outcomes was gathered. During the 90-day follow-up second phase mortality and readmissions were sought. Multivariate odds ratios (OR) were calculated to evaluate factors associated with multiple admissions.
Results: Data on 14,456 cases are reported, of which 6,821 (47.2%) were the first admission (countries range 29.3-74.5%). Patients characteristics associated with multiple previous admissions were: current smoker (OR 0.69), FEV_1 value (OR 0.99), and PO_2 value (OR 1.003). Health care proved to multiple admission patients was different in terms of chest x-ray not done (OR 2.03), methylxanthines use (OR 1.2), antibiotic use (OR 0.78), diuretics use (OR 1.16) and use of NIV (OR 1.11). Reports at discharge tended to have a higher use of theophylline (OR 1.23), oxygen (OR 1.8) and mechanical ventilation (OR 1.5). We also found an impact on readmission rate (OR 0.4).
Conclusions: Multiple admission patients represent a different type of COPD patient admitted to hospital, with a more severe disease requiring more resources.

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Emergency oxygen use and monitoring in the pre-hospital and acute hospital setting – The significance of a common problem

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Introduction: Evidence shows that oxygen (O_2) can cause decompensated type 2 respiratory failure (T2RF) increasing morbidity and mortality in COPD patients.
Aim: To review pre-hospital and emergency hospital use of O_2 in COPD patients.
Methods: All COPD admissions in January 2011 to Worcester Royal Hospital were audited against BTS guidelines.
Results: Ambulance documentation showed no record of previous NIV or O_2 alert card. There is no box to record FiO2 on the ambulance data form. O_2 dose (51.6%) and mask (48.4%) recordings were suboptimal. 60% of patients were given 28% venturi masks and 13.3% non-rebreathe masks. 45.8% of patients were given O_2 with adequate saturations (sats). 72% of patients given O_2 had sats > 92%.
In hospital, 9.5% of clerkings contained a history of prior NIV. 2/3 of patients with adequate sats were given O_2. 80% of those on O_2 had sats above 92. 36.7% of patients had O_2 prescribed with 45% having correct sats ranges. 15 patients had T2RF; 5 with sats > 92%. 3 patients met the criteria of NIV; all had sats > 92%. Mean length of stay (LOS) was 6 days longer in those who had NIV. 90.5% of discharge letters did not contain an ABG result.
Conclusions: There is still a major issue with O_2 use and monitoring in COPD patients. Patients are being given too much O_2, it is not prescribed and not being documented accurately. This causes increased morbidity and cost, evidenced by those with hyperoxia developing T2RF and longer LOS. We recommend the ambulance data form includes an FiO_2 box, O_2 prescription is mandatory, documentation is improved and discharge letters include an ABG. Doctors, nurses and paramedics should all be regularly educated in O_2 therapy.

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An audit of inpatient mortality and readmission rates in acute exacerbation of COPD – Exploring the role of comorbidity and inflammatory markers

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Acute exacerbations of COPD is the cause of rising admissions and burden on resources in spite of systems to minimise inpatient stay and facilitate discharge. The system of reimbursements in the UK NHS, penalises hospitals for readmission within 30 days. Understanding the factors leading to early readmission may help to focus resources.
We audited inpatient records of 577 (female = 260) episodes in 12-months till Dec'11. Age, co-morbidities, length of stay (LoS), readmission rate, time to readmission, white cell count and C reactive protein were collected.
218 episodes with >1 admission, 47% readmissions within 30 days; and 20 inpatient deaths. Age 69 (±11) yrs men & 72 (±12) yrs women, p=0.02. The LoS = 6 (±7) days men & 7 (±10) days women, p=ns. 344 patients had >1 associated co-morbidity. Standard mortality was 35/1000 admissions.
Patients who died were older (76±8 vs 70±11 yrs, p = 0.03) had higher (WCC 26±26 vs 12±7 x10-9/l, p <0.001; CRP 78±100 vs 44±57 g/l, p = 0.01). A higher LoS was predicted by (WCCmax Lin regr coef B 0.118, p=0.005; CRPmax B 0.114, p=0.04) and age (Spearman's rho 0.19, p<0.001). Time to readmission was not predicted by any of the above parameters.
Inpatient mortality and LoS were predictably correlated with age and raised inflammatory markers. Nearly half of the patients were readmitted within 30 days, which would lead to morbidity and a loss of revenue. Yet, none of the common factors were found to predict the 'risk of', or 'time to' readmission. Therefore, future prevention of admission strategies may need to include telemedicine, monitoring at home and frequent flyer clinics.

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Differences between men and women COPD admissions: Evidence from the European COPD audit

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Introduction: Studies using administrative data from N America provide conflicting results for gender survival differences in COPD (Machado 2006, Gonzalez 2011). We used clinician collected data to look at Hospital and 90 day survival following admission with COPD exacerbation.
Method: The European audit programme collected retrospective data from clinical case notes and telephone enquiry from 15,821 patients admitted between October

2010 and February 2011 in 13 European countries. Data was entered onto a web collection tool and analysed centrally.
Results: Women admissions were in a minority (39.1% P<0.001) but proportion of all admissions varied from 53% in the UK to only 14% in Spain. Women were more likely to be non-smokers than men (9.6 vs 3.4%), had lower pack year histories if smokers (23.5 vs 31.1) but were more likely to be current smokers (37.5 vs 28.3% P<0.001). They were less likely to have increased sputum (60.9 vs 66.6%) or coloured sputum at admission (53.5 vs 56.3% P<0.001) and less likely to receive steroids or antibiotics (P<0.001). Women had fewer co-morbidities (1.3 vs 1.7 P<0.001) but were more likely to die in hospital (5.5 vs 4.7% P=0.018) an effect carried over to 90 days (5.6 vs 6.4% P=0.008) but had shorter length of stay and were less likely to be readmitted if discharged successfully (32 vs 34% P=0.004).
Conclusions: These data suggest women exhibit different COPD characteristics and have a higher mortality when admitted to hospital.
Machado Am J Respir Crit Care Med 2006;174:524. Gonzalez Thorax 2011;66:38.

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Acute exacerbation of COPD is associated with three-fold elevation of cardiac troponin T

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Several studies have shown that elevated levels of cardiac troponin T (cTnT) in patients hospitalised for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is associated with dismal prognosis. The aim of the present study was to compare cTnT in patients hospitalised for AECOPD with cTnT among chronic obstructive pulmonary disease (COPD) patients in stable state.
The index group (N=50) were hospitalised due to AECOPD. They had a confirmed diagnosis of COPD before admission to the hospital. The references (n=124) were recruited from a hospital for pulmonary rehabilitation. They all had COPD in a stable state. High-sensitivity cTnT was measured within the first day of admission for AECOPD. The cumulative tobacco consumption in the index group and the references was 43 and 33 pack-years, respectively. Similarly the FEV_1/FVC-ratio in the index group and the stable state was 40% and 47%, respectively.
The geometric mean of hs-cTnT in the index group was 25.8 ng/L (95% confidence interval (CI): 21.1 – 31.7) compared with 4.5 ng/L (95% CI: 3.7 – 5.5) in the reference group. Multiple linear regression analyses showed that the ratio between hs-cTnT in AECOPD-patients and the references was 3.40 (95% CI: 2.30 – 5.02) and that hs-cTnT increased 1.34-fold (95% CI: 1.16 – 1.54), 1.24-fold (95% CI: 1.07 – 1.44) and 1.14-fold (95% CI: 1.00 -1.29) for each quartile increase in leucocyte count, age and creatinine, respectively. A significant univariate association between cTnT and arterial hypoxemia was also found but this association attenuated almost to a zero-effect after inclusion of relevant covariates.
AECOPD is associated with elevation of hs-cTnT compared to stable COPD.